UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICALS INDUSTRIES LTD., TEVA NEUROSCIENCE, INC. and YEDA RESEARCH AND DEVELOPMENT CO. LTD.,

Plaintiffs,

v. 08-CV-7611 (BSJ)

SANDOZ, INC., SANDOZ INTERNATIONAL GMBH, NOVARTIS AG, and MOMENTA PHARMACEUTICALS, INC.,

Defendants.

TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICALS INDUSTRIES LTD., TEVA NEUROSCIENCE, INC. and YEDA RESEARCH AND DEVELOPMENT CO. LTD.,

Plaintiffs,

v. 09-CV-8824 (BSJ)

MYLAN PHARMACEUTICALS INC., MYLAN INC., NATCO PHARMA LTD.,

Defendants. Non-Jury Trial

New York, N.Y.
September 15, 2011
9:30 a.m.

Before:

HON. BARBARA S. JONES,

District Judge

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ALSO PRESENT: CORT CHASE, Litigation Support

THE DEPUTY CLERK: All rise.

THE COURT: Good morning. Please be seated.

Come on up, Dr. Rice.

MS. BLOODWORTH: Before we start, I just have a couple matters.

THE COURT: Sure.

MS. BLOODWORTH: Your Honor had ordered us to produce the empower data to plaintiffs a couple days, and I just wanted to provide you with a letter showing that we had done so.

THE COURT: Okay, fine.

MS. BLOODWORTH: We were able to provide it yesterday, the underlying data for what we produced in June.

THE COURT: Okay, great.

All right, Mr. Jones.

MR. JONES: Thank your, your Honor.

SUSAN A. RICE,

called as a witness by the defendant,

having been previously sworn, testified as follows:

DIRECT EXAMINATION

BY MR. JONES:

Q. All right, Dr. Rice, let's pick up. Just for context, the Court has accepted you as an expert in the field of toxicology, so now we're going to get into the substance of your opinion, all right, your work?

A. All right.

Q. Dr. Rice, what's your understanding as to when the applicants applied for the '808 patent?
A. It was May, 1994.
Q. And have you been asked to define a person of ordinary skill in the field of toxicology as of May of 1994?
A. Yes, I have.
Q. And what is your definition of a person of ordinary skill in the field of toxicology?
A. A person of ordinary skill in the field of toxicology would be one who has a Ph.D. in toxicology or a related field, and has three to five years of experience, practical experience after the Ph.D.
Q. Now, Doctor, I know that from our discussion yesterday you have some 30 years of practical experience in toxicology. So I'm going to ask you to keep in mind when I ask you questions this morning, I want you answering from the perspective of a person of ordinary skill in the art of toxicology, unless I ask for something different. All right?
A. All right.
Q. Very well. Now, I understand you're not a lawyer, so. You were also asked to make some assumptions regarding patent law principles as they apply to your work in this case, is that right?
A. That's correct.
Q. All right. And what were those assumptions that you were

asked to make?
A. I was asked to make three assumptions, and the first is that the '550 patent is prior art; the second that the 1987 clinical article by Bornstein, which was published in the New England Journal of Medicine is prior art; and, third, in determining whether unexpected results have been shown, the legal test is whether there is a difference in kind, and not just degree compared to the prior art.
Q. Doctor, why don't you flesh out a little bit about what you -- how you understand that difference in kind versus difference in degree test, what that means to you from the perspective of a person of ordinary skill in the art as you reviewed the materials?
A. To me a difference in kind is where there is significant, very significant difference in the findings; in this case in the toxicity of the agent. And --
THE COURT: Excuse me, Dr. Rice.
Mr. Jones, why don't we just get into the meat of the testimony.
MR. JONES: Sure.
MR. WIESEN: Thank you.
Q. In providing an opinion in this case, Doctor, have you reviewed the '550 patent and the Bornstein study?
A. Yes, I have.
Q. And have you reviewed the toxicity study or analysis that's

contained in the specification, the common specification for the '808 and other patents in suit in this matter?
A. Yes, I have.
Q. Now, have you been asked to render an opinion in this case regarding whether a person of ordinary skill in the art of toxicology would have found that the claimed copolymer-1 in any form exhibit unexpectedly lower toxicity in the prior art?
A. Yes, I have.
Q. And what is your opinion on that issue?
A. My opinion is that a person of ordinary skill in the art of toxicology would not have found that the claimed copolymer-1 compositions in any form would have exhibited unexpectedly lower toxicity compared to the prior art.
Q. All right. Now, for purposes of your work and your opinion, did you perform your own independent experiments, toxicological experiments or studies on copolymer-1?
A. No, I did not.
Q. What did you do to come to your opinion?
A. To come to my opinion, I looked at the patents and the references therein, I looked at the references, and then I also looked at Teva Bio-Yeda, and the Weizmann Institute documents and related documents.
MR. JONES: Mr. Russell, may we see PTX-1, the '808 patent?
Q. Doctor, you indicated that the '808 patent is one of the

patents that you reviewed in the course of coming to your opinion in this case, is that correct?
A. That's correct.
Q. All right. Now, the first reference, we talked about this, mentioned it already. The first reference that we're going to talk about is the '550 patent, correct? You see that on the face of the patent?
A. Yes, I see that.
Q. All right. If we could have up PTX-26, the '550 patent, which has previously admitted in this case.
All right. Now, Dr. Rice, you were here for Dr. Zeiger's redirect testimony yesterday?
A. Yes, I was.
Q. And in that redirect you heard that he testified about PTX-17 at TEV304384 in which Teva stated that the '550 patent teaches a copolymer-1 with a minimum molecular weight of ten kilodaltons?
A. I understand that, yes.
MR. WIESEN: Objection, your Honor. I think the transcript speaks for itself in terms of what the documents say. I'm not sure why we need to read them into the record.
THE COURT: I assumed she needs a reference point for her testimony. But is that -- are you saying that's not accurate?
MR. WIESEN: I think it wasn't quite exactly what the

document reflected, but if it's just for the context for the witness --

MR. JONES: If you want, I can have the exhibit pulled up so we have the precise wording if the Court would like?

MR. WIESEN: If it's just for the reference, then we can just move things along, then.

THE COURT: Okay.

MR. JONES: Very well.

THE COURT: What are you referring to, though?

MR. JONES: We're referring to the document from the filed history that Dr. Zeiger talked about in his redirect where, which had the statement from Teva that the '550 patent teaches a copolymer-1 with a, I believe it was with a minimum --

THE COURT: Prosecution history?

MR. JONES: Yes, ma'am.

THE COURT: Okay, fine.

MR. JONES: Yeah, with a minimum molecular weight.

THE COURT: I just wasn't sure what you were talking about.

MR. JONES: Right, that history of minimum of ten kilodaltons.

THE COURT: Okay.

Q. All right. And, in fact, is that consistent with what you were asked to again assume as part of your giving your opinion

that the '550 patent described a copolymer-1 that has at least at the lower range starting about ten kilodaltons?
A. Yes, that's what I understood.
Q. Now, what is your understanding of the molecular weight range claimed in the '808 patent?
A. I understand that weight range to be five to nine kilodaltons.
Q. Now, I'm going to ask you -- I know you're not a copolymer peptide chemist, so I'm asking you from the perspective of a person of ordinary skill in toxicology. What would you expect to be the difference in the toxicity profile between the range claimed in the '808 patent, and the low end of the range described in the '550 patent?
A. I would expect that the molecular weight ranges between the two, the five to nine composition and the lower ten would overlap probably considerably. And where they didn't overlap, I would expect them to essentially butt up one against the other. So I would not expect any significant difference in the toxicity profile between the two compositions.
Q. All right.
MR. WIESEN: Your Honor, I have to -- that's outside the scope of this expert's or this witness' expertise, so I I'm going to move to strike.
THE COURT: That is true.
MR. JONES: We're just focusing on what you would

expect as to the toxicity profile between the two ranges.

THE COURT: I didn't hear anything about toxicity.

MR. JONES: Okay, let me make -- may I rephrase the question, then, so it's clear?

THE COURT: All right, let's hear it.

MR. WIESEN: Your Honor, not to cut off Mr. Jones, but even that, given the differences we've heard about the ways that the average molecular weight are measured, and the fact that that distinction can matter here, I think the ability of this witness with her expertise couldn't even make this comparison.

THE COURT: I haven't heard why the witness believes that either she would know why there would be a toxicity difference or no difference in these ranges. I mean, I'll hear it, but so far I don't know how she can opine on this, okay.

MR. JONES: Right.

Q. From the perspective of a person of ordinary skill in toxicology, I'm simply asking you -- I'm not asking you to evaluate molecular weight range overlap. But given a range of five to nine and a low range that starts at ten, what's your perspective as to whether there would be a change or whether you would expect to see a change in the toxicity profile at that point of --

THE COURT: I don't know what the foundation is for this.

Q. Is it, as part of your work as a toxicologist is it, do you evaluate toxicity profile of agents?
A. Yes, I do.
Q. And do you have experience in assessing the toxicity profile of agents in different doses?
A. Yes, I do.
Q. In different compositions?
A. Yes, including polymers.
Q. And so in polymers in different weight ranges?
A. Yes.
Q. Given that experience, what would you expect to see as to the -- in regard to the toxicity profile between the '808 patent and the low end of the '550 patent, what would you expect to see?
A. I would have no expectation that they would be -- that the toxicity profile would be significantly different from one to the other.
Q. And have you reviewed any Teva documents that support this understanding?
A. Yes, I have.
MR. JONES: Mr. Russell, please call up DTX-1250.
Q. Dr. Rice, did you review DTX-1250 in the course of forming your opinion in this case?
A. Yes, I did.
MR. JONES: Note for the Court that DTX-1250 was I

believe previously admitted in the testimony of Doctor, Mr. Congleton.

Q. Dr. Rice, what is DTX-1250?

A. DTX-1250 is a Teva document, essentially, an open letter to whom it may concern, and it was written or signed on November 10th, 2005.

Q. Please read into the record the portions of DTX-1250 that you believe support your conclusion that you would -- that there would not be -- that you would not expect to see a change in the toxicity profile between the '808 nuclear weight range and the low end of the '550?

A. The first place is "In the marketing authorization submission, the average molecular weight of the active substance was in the range of 4,700 to 13,000 daltons. However, upon request of some concerned EU member states, the average molecular weight was brought down to the range of 5,000 to 9,000 daltons."

Q. Okay, let me stop you. And is that your understanding of basically the range that's claimed in the '808 patent?

A. Yes, that is my understanding.

Q. All right. Go ahead, please.

A. "The change in the average molecular weight of the active substance has no implications on the safety and chemical characteristics of the concerned medicinal product."

Q. Now, Doctor, what conclusion do you draw from this Teva

document?
A. From this document, I would conclude that there was no significant difference in toxicity profile of the compounds in the range of 4,700 to 13,000 daltons, and those from in the range of 5,000 to 9,000 daltons.
Q. Now, Doctor, I note you mentioned toxicity. The letter talks about safety. How are those two concepts related from the perspective of a person of skill in the art in toxicology?
A. Safety, in general, there isn't one definition. But, in general, to a regulatory body such as the FDA would mean the balance of risk and benefit.

In this case, in the human condition, there would be what I read here is that there is no expected difference between the two, the two different ranges in the toxicity that is seen in the human population.
Q. All right. Let's go back to the '550 patent.

Doctor, what does the '550 patent, what would that tell a person of skill in the art of toxicology about toxicity of compounds claimed in the '550 patent or described?
A. I found no mention of toxicity in the patent, although one might assume that there is no significant toxicity. It's not stated, however.

MR. WIESEN: Objection, your Honor. I move to strike after the word "assume."

THE COURT: All right.

Q. Dr. Rice, let's go back to the '808 patent we saw earlier, PTX-1. Does it refer to any other studies that provided information on toxicity of copolymer-1?
A. Yes, it did. It referred to the study by Bornstein published in 1987 in the New England Journal of Medicine.
Q. So we have a clear record, are you looking at column one of the '808 patent, lines 26 through 31?
A. Yes, I am.
Q. All right. Well, did you discuss the Bornstein 1987 study in your report; is that a document that you reviewed for purposes of giving your opinion?
A. Yes, I did.
Q. All right showing you PTX-31. Is this the Bornstein study that you discussed in your report?
A. Well, this is actually the table of contents from the Journal that contains the Bornstein study. I believe on the next page we have the start of the Bornstein study on page 408.
Q. Very well.
MR. JONES: I'll note for the Court that PTX-31 was admitted during the direct testimony of Dr. Arnon.
Q. Dr. Rice, where does the Bornstein study first discuss toxicity information?
A. Toxicity information is discussed on the first page, second column.
Q. All right. And can you read into the record the language

from the Bornstein study from 408 that describes or discusses toxicity information?

A. "Cop-1 is also nontoxic during short-term and longer term, three to six months, administration in mice, rabbits, and dogs."

Q. Now, Doctor, I understand that that's simply a single sentence and you can't draw definitive conclusions from that. But from the perspective of a person of skill in the art of toxicology, what does that sentence from the Bornstein study suggest to you about the toxicity of copolymer-1?

A. To a person of ordinary skill, it suggests that, first of, all studies in these various species have been conducted, and no significant effects were found.

We know that before drugs are administered to individual patients, that there is certain amount of preclinical testing in animal species that is performed.

And so it would I would surmise that these were the preclinical tests that they were talking about.

Q. All right. And if the description of short-term and longer term -- again I know you can't draw definitive conclusions because you're only discussing the actual findings, but what type of -- what is described as a short-term and a longer term study; what does that mean to a person of ordinary skill?

A. A short-term study would be one where the agent is administered one or several times over a short period of time,

maybe up to as long as a week. And then the longer term studies, as it says here, would be about three to six months. And this is usually what is required to be administering drugs to a patient for more than just a few days.

Q. Finally, Doctor, with regard to this sentence, the fact that cop-1 was shown to be nontoxic in mice and rabbits, and dogs, would that suggest -- again without -- you won't be able to draw firm conclusions, but what does that suggest about repeatability of the non-toxicity determination for copolymer-1?

A. It suggests that we're finding or they are finding non-toxicity in more than one species, and that is usually what is required by the FDA and other agencies before, again, a drug is administered to humans.

Q. Dr. Rice, is toxicity information provided in any other part of PTX-31, the Bornstein 1987 study?

A. Yes, it is. There's a section on laboratory studies and side effects.

Q. All right. We're moving to four, page 412 of the Bornstein 1987 study; is that correct?

A. Yes.

Q. All right, Doctor, what part of 412 and what part of page 412 would we find information of interest to a toxicologist?

A. A toxicologist would be interested in the blood and urinalysis that was performed on these patients during the time

that they were administering or self administering the drug.
Q. All right. Just so again we have a clear record, are you referring to information conveyed under the laboratory studies and side effects section on page 412 of the 1987 Bornstein study?
A. Yes, I am.
Q. Dr. Rice, what would a toxicologist conclude after reading the urinalysis and blood examination information contained in the Bornstein study?
A. That there were no toxic effects manifest in the copolymer-1 treated group, or in the placebo treated group. There are no, essentially, no differences between the two groups, and there was no effect that was noted on the various tests of liver function and also blood parameters.
Q. Dr. Rice, is there any further discussion about side effects of copolymer-1 in the Bornstein study?
A. Yes. There were several side effects that were noted. The first is the injection site reaction, which was seen in a number of the patients. It was also seen in some placebo, but primarily in the copolymer-1 administered patients.

And then there was there were other side effects that were noted to various degrees such as nausea, headache, that sort of thing. But those side effects did not rise to the level of toxic effect, because there was no significant difference between the two groups.

Q. The two groups, I'm sorry, just the two groups meaning the placebo group and?
A. The placebo group and the copolymer-1 treated group.
Q. All right.
A. In addition, there were two patients that were noted during the course of study to exhibit what Dr. Bornstein has called the vasomotor response. And it is unclear what -- and this, these were both copolymer-1 treated patients. It is unclear as to the exact mechanism for this. We would call it, generally, an idiosyncratic reaction, in that it is unclear what it is related to. Bornstein had mentioned that there might be some allergic basis to it, but I don't think that was actually determined.
Q. So just so that we're clear, the injection site reactions to these side effects of the vasomotor affects, how does that affect a toxicologist's view as to whether copolymer-1 one is toxic or nontoxic?
A. I would not consider those to be toxic effects. The injection site reaction is a reaction of the drug at the site, and it would not directly pertain to the systemic toxicity, which is more what we're interested in.
Q. Dr. Rice, does the Bornstein 1987 study tell you the molecular weight of the copolymer-1 composition that was used in the study?
A. Yes, it does.

Q. Could we go to 408 of PTX-31?
A. On the first page, the first paragraph of the actual article, we see that the molecular weight range is listed as 14,000 to 23,000 daltons.
Q. All right. So what would a person of skill in the art of toxicology conclude about copolymer-1 and the range from 14,000 to 23,000 daltons, what would they conclude as to copolymer-1's toxicity in this weight range?
A. A toxicologist would conclude that there is no toxicity that is evident in humans in this particular range.
Q. All right, let's go back to the '808 patent, PTX-1.

Can you please turn with me to example two in the '808 patent specification. And, again, this is the common specification for the patents in suit. We're at column three, line 20.

Dr. Rice, what is being described in example 2A of the '808 patent specification?
A. Example 2A describes the in vivo toxicity analysis.
Q. And what is meant by in vivo?
A. In vivo, essentially, means in life or in the whole body.
Q. Can you please describe for us the in vivo toxicity test as it's explained or described in example 2A of the common specification?
A. Yes. This particular test is conducted in mice, and different batches of an agent -- in this case copolymer-1 --

are tested in five mice. Each of those mice is injected intravenously with 1 milligram of the copolymer-1 batch. They are subsequently monitored for a period of 48 hours, and specific observations are made at ten minutes, 24 hours, and 48 hours, and they are looking for adverse effects, the worse of course is death.

Q. You mentioned that these animals were monitored for a 48 hour period, is that correct?

A. That's correct.

Q. Is that for a toxicologist, would that be considered a short-term or longer-term study?

A. This is a short-term study.

Q. All right. You indicated that the testers were looking for adverse effects, the ultimate one of which of course is death. But what would a toxicologist understand other adverse effects to potentially be?

A. In this particular test, one is limited to things that can be observed by eye in the small animal amounts. So the things that might be observed would be convulsions, hyperactivity, staggering gate, other things of that nature.

Q. And I note that, Doctor, or you noted that the drug is administered intravenously in this test, is that correct?

A. Yes, it is.

Q. Would an intravenous injection mechanism of administration, is that going to allow the testers to determine, make any

determinations about injection site reactions?
A. No, you would not be able to determine injection site reactions, unless the compound might be very caustic.
Q. And I should make clear, in the usual -- in your review of the Bornstein study, what is the usual method of delivery of copolymer-1 through an injection?
A. Copolymer-1 in patients is administered subcutaneously.
Q. All right. Going back to the example 2A study, tell me how the study defined toxicity?
A. The study defined toxicity as any adverse effect, including death, that occurred in any of the five mice tested for a batch. So if one mouse tested with the batch exhibited adverse effects, including death, that particular batch would be declared toxic. And if no mice for a particular batch exhibited adverse effects, then that batch would be designated as nontoxic.
Q. All right, let's take a look at the batches that are described -- if we could have highlighted the first paragraph of the example 2A. Thank you.
Doctor, what are the molecular weights of the batches that were tested or that are reported tested in example 2A?
A. There are three batches of copolymer-1 that were tested, and their molecular weights were 7.3, 8.4 and 22 kilodaltons.
Q. And was there also a distinction between the batches in regard to what's called species?

A. Yes. Two of the batches had less than 2.5 percent copolymer-1 species greater than 40 kilodaltons. Those are the 7.3 and the 8.4 batches. The higher molecular weight batch 22 kilodaltons was described as having more than 5 percent copolymer-1 species over 40 kilodaltons.

Q. All right, now let's go to the last paragraph of example 2A, and please describe how the test reported the results of the toxicity in vivo test?

A. Two batches with the average molecular weight of 7.3 and 4.8 kilodaltons were designated as --

Q. I'm going to stop you. I think you said 4.8. Did you mean --

A. Did I say 4.8? It's 8.4, thank you.

Q. Go ahead.

A. Were both designated nontoxic, and the batch at 22 kilodaltons average molecular weight where three out of the five mice died was designated as toxic.

Q. So based on how the toxicity information or the in vivo information is presented in the patent, what would a toxicologist, what conclusions might a toxicologist draw regarding the toxicity of copolymer-1 in the five to nine molecular weight range versus an above five to nine range?

A. From the information that's given here, it certainly looks as if the five to nine molecular weight range would not be considered toxic; whereas above ten would be considered toxic

because of the 22 kilodalton batch.
Q. And what about again -- same question in regard to the species, the less than 2.5 percent copolymer-1 species over 40 KDa versus the more than 5 percent copolymer-1 species over 40 KDa?
A. From the information we have, it looks very much as if the less than 2.5 copolymer species over 40 kilodaltons is nontoxic; whereas the batch containing greater than 5 percent of the -- greater than 5 percent of the copolymer-1 species over 40 kilodaltons is toxic.
Q. Doctor, what would a toxicologist assume about the characteristics of the three batches that are analyzed in example 2A?
A. Because this is medical product that is being talked about, a toxicologist would assume that all of the batches being analyzed are the final product.
Q. Now, are you personally or professionally experienced with in vivo tests like that described in example 2A?
A. Yes, I am.
Q. And what's the general utility of such a test?
A. The test is somewhat limited in the information that you can gain, because there is only direct observation, and one of the end points being death. But, nevertheless, you can get some information as, I mentioned before, if there were convulsions or hyper activity, something of that nature, that

could be picked up.

But overall, it gives you little information in the way that it's conducted.

Q. All right. Doctor, in reviewing the materials in this case, including Teva documents, did you find a document that augments your understanding of the toxicity analysis contained in example 2A?

A. Yes, I did.

MR. JONES: I'd like Mr. Russell if you put up DTX-419 or 3149T.

Q. And from 3149T, we're looking at Bates TEV122355-RC.

MR. JONES: And I'll note for the Court that this version of DTX-3149T, which represents a translation of 3149, was admitted during the July testimony of Dr. Pinchasi.

THE COURT: Thank you.

Q. All right, Doctor, is this document, is 3149T a document that you reviewed in the course of your work in this case?

A. Yes, it is.

Q. What is being depicted in 3949T, what is this?

A. It is a table that contains 13 batches of copolymer-1 one of various molecular weights, which average molecular weights which we see in column two that range from 6,000 250 daltons to 22,000 daltons. And then there is information regarding some other parameters, and then the safety in vivo test.

Q. Column five?

A. Column five is the safety in vivo test, which is the same test that we were previously talking about.

MR. JONES: Would you, Mr. Russell, if you would, please pull up a side-by-side of Exhibit 2 or of example 2A from the '808 patent, and the first page of DTX-3149T?

THE COURT: Mr. Wiesen.

MR. WIESEN: Your Honor, I'm not sure exactly where he's going here, but we had a trial on the inequitable conduct issues in July, which seems to be where we're going. The defendants have rested on that issue. Dr. Rice was initially on their witness list for that trial. They opted not to call her.

So we're going to object, to the extent they're going into testimony that's relevant to inequitable conduct, rather than on unexpected results, which is where Mr. Jones appears to be going.

MR. JONES: And we accept that. This is not about blame or who should have or who would have. Its just about toxicity information.

THE COURT: All right. Well, I'll hear it.

MR. JONES: Very well.

Q. Now, Dr. Rice, is it your assessment after listening to the testimony of Dr. Pinchasi and others, is it your assessment that DTX-3149T, that the test described there are the tests that's depicted in example 2A of the common specification?

A. Yes, that is my understanding.
Q. And do you see any batches from 3149T that are depicted in example 2A?
A. Example 2A has three batches that are also shown in the April '94 data table.
Q. All right, which ones are those?
A. It is the second and third batch, and then the final batch.
Q. So that's the 7300 molecular weight, the 8400 molecular weight and the 22,000 dalton molecular weight are depicted in 3149T, as well as in example 2A?
A. That is correct.
Q. All right. Now, Doctor, does 3149T depict any molecular weights between 8400 and 22,000, any batches with molecular weights?
A. Yes, there are nine batches that are evidenced here between 8400 and 22,000 daltons.
Q. And in those nine batches, how many of those batches report that mice died in the safety in vivo test?
A. Of these nine batches, none of them report any deaths in the mouse in vivo safety test.
Q. Would you please read into the record, or actually I probably could do this quicker. So I will simply read into the record those weights, and you can confirm for me.
So zero mouse died are 9250?
THE COURT: Mr. Jones, I know what they are.

MR. JONES: Okay. Very well.
THE COURT: I can read.
MR. JONES: That's super.
THE COURT: You've identified where they are.
MR. JONES: Thank you, your Honor.
THE COURT: Thank you.
Q. Now, Dr. Rice, is it your understanding of having again reviewed materials outside in preparing your report, that some of the batches in 3149T were rejected batches of copolymer-1?
A. Yes, that's my understanding.
Q. And which batches are those?
A. Those are the ones that start at 04592. There are three batches.
Q. So 04592, 04692, and 04492, those are -- those were rejected batches of copolymer-1 one?
A. Yes. It is my understanding they were rejected on the basis of their chromatographic profile in the select B column.
Q. All right. And as to -- do you have an understanding as to whether some of the batches depicted on 3149T were marker batches?
A. Yes. The last three batches were marker batches, starting 196/2, and then going through 186/1.
Q. All right. And do you see -- you can take off the green, thank you -- do you see any batches with the prefix 123?
A. Yes, I do.

Q. And based on, again, your review of information provided in this case, what's your understanding of what the 123 prefix means in regard to a batch of copolymer-1?

A. My understanding is all of these batches are a final formulated product.

Q. Now, Dr. Rice, does example 2A contain molecular weight batches from identical product batches?

MR. WIESEN: Your Honor, there is no doubt now we're headed into inequitable conduct. I object to this line of questioning.

MR. JONES: If you about give me conditional relevance -- in fact, I'll ask the predicate relevance question, then you'll see this is relevant to a toxicologist's understanding of the reliability of the 2A example.

MR. WIESEN: The reliability of the 2A data was part of the issue in the inequitable conduct trial. We're talking now about unexpected results which, quite frankly, aren't just limited to what's in the patent.

THE COURT: No, I know. I don't expect to see this argument in the inequitable conduct.

MR. JONES: Of course not. Of course not.

THE COURT: Go ahead.

MR. JONES: Thank you, your Honor.

Q. All right. As a toxicologist, I think you mentioned it earlier, but what a toxicologist has confidence in a study,

what does a toxicologist expect in regard to the characteristics of tested batches?

A. The only way that one can properly compare different batches of molecular weights or anything else, is to have the various batches controlled, so that the only variable being tested is that of molecular weight and nothing else.

So I would want to see all of the batches prepared in, essentially, the same way to essentially be prepared the same way as the final formulated product is.

Q. Now, when we look at example 2A, 2A reported the results of the 7300 and the 8400 or dalton batches, correct?

A. That's correct.

Q. And were those, from your understanding, are those final product batches?

A. My understanding is that they are final product batches.

Q. And then it's reported that 22 KDa result, correct?

A. Yes. And the 22 KDa result is from a batch that has been found to be a marker batch.

Q. Now, and I know that you're not an expert on the composition of marker batches versus final product batches, but what does that do to the confidence of a toxicologist's understanding that final product batches were prepared with a non-final product batch?

MR. WIESEN: Objection, your Honor. He just said you're not an expert in this, but what does it mean. There is

no foundation for this question.

THE COURT: There isn't.

Q. What does it do to your confidence as a toxicologist if batches -- if non-final product batches are compared to final product batches?

MR. WIESEN: Same objection, your Honor.

A. As a toxicologist --

THE COURT: Just a minute.

THE WITNESS: I'm sorry.

THE COURT: That's okay.

If she doesn't know what a marker batch is, I don't understand the question.

MR. JONES: Well, if she understands that a marker batch is not a final product batch --

THE COURT: Well, do you?

THE WITNESS: Oh, yes, I do.

THE COURT: Okay.

Q. All right, I'll get that on the record. Do you understand, from having read testimony and expert reports in this case, that marker batches differ or are different from final product batches?

A. Yes, I do understand that.

Q. So given that predicate, how does it affect the confidence of a toxicologist to understand that final product batches were compared with marker batches?

A. It certainly gives me no confidence. Because I expect the batches to be prepared in the same manner so there might not be any other factors introduced that could influence the toxicity.
Q. Now, we've been talking about this need for comparing directs to directs.
Dr. Rice, you indicated that there were four, four copolymer-1 batches depicted on 3149T from final product batches, correct?
A. That is correct.
Q. And what are the molecular -- we've already talked about 7300 and 8400. What are the other two?
A. The other two are 6,250, and 10,950 daltons.
Q. And how many mice died in the 10,950 batch of copolymer-1?
A. No mice died in this particular batch.
Q. And so under the definition of toxicity that's provided in example 2A, is the 10,950 batch of copolymer-1 toxic?
A. It would be designated as nontoxic.
Q. Well, is that -- and as a toxicologist, is that a batch of 10,950 being declared nontoxic or being found nontoxic, is that consistent with the claim that copolymer-1 in a molecular weight of five to nine kilodaltons exhibits lower toxicity in the prior art?
A. No, it --
MR. WIESEN: Objection, your Honor. This is now clearly the inequitable conduct argument. He's talking about

one batch and the consistency of statements between what's in the patent and the results in the one batch in the April '94 data table. It's hard to see how it's anything but.

THE COURT: I think we'll be through this faster if we just hear it.

MR. JONES: Thank you, your Honor.

Q. And, Dr. Rice, just -- I take it that you earlier described the less than 2.5 percent copolymer-1 species associated with the 7.3 and the 8.4; you remember that?

A. Yes, I do.

Q. Versus the in the higher -- the five, the greater than 5 percent copolymer-1 over 40 KDas species; you remember that?

A. Yes, I do.

Q. Now having a full understanding of the information provided or at least of the testing that occurred, the in vivo testing, what can you -- what would a toxicologist conclude about whether it had been shown that less than 2.5 cop-1 had -- was lower -- was unexpectedly lower than greater than 5 percent cop-1?

A. When I look at all of the information, and from actually example 2B, I have additional information about the molecular weight species of 13,000 and 14,500. We can now see on this table where the 13,000 and 14.5 batches were shown to have greater than 5 percent of molecular weight species of copolymer-1, with molecular weights over 40 kilodaltons.

Q. And how many mice died in the 13,000 and 14,000 five batches of copolymer-1?
A. No mice died in either of those batches.
Q. Now, looking further at DTX-1349, I note that the table reports percent RBL release; do you see that?
A. Yes, I do.
Q. And what is percent RBL release?
A. That, essentially, refers to release of serotonin or histamin from this particular cell.
Q. And what does the 1994 data tell you about the relative utility of the RBL test in the in vivo test in assessing toxicity?
A. This particular RBL test compared to the in vivo tests shows me that there is no correspondence between the two. We have various values for the RBL that are shown across the molecular weights; whereas, we have zero out of five animals died; batches were declared nontoxic from 6,250 all the way to 14,500, or I should more accurately say that these batches would meet the criteria for being designated as nontoxic.
Q. Now, you'd agree that the RBL percent release appears to be getting bigger as the molecular weights get bigger, correct?
A. I think -- there's quite a bit of variability here, so it isn't a consistent increase, although at first glance it would look as if there might be an increase.
Q. But are you seeing any consistent results as linking

increase of RBL release and mice that died?
A. No, I see no relationship there.
Q. All right. Now, have you reviewed any internal Teva documents discussing the relative utility of the RBL and in vivo safety tests?
A. Yes, I have.
MR. JONES: Mr. Russell, can I have DTX-1256.
Q. Dr. Rice, is DTX-1256 a Teva document prepared by Dr. Pinchasi that you relied on in your expert report?
A. Yes, it is.
MR. WIESEN: Objection, your Honor.
THE COURT: Mr. Jones, I do have to say -- I mean I would have been very happy to hear this during the inequitable conduct trial. What am I supposed to do with it now?
MR. JONES: Your Honor, it's simply -- we're just talking about the reliability. What they have to show is unexpectedly lower results. They are predicating their assertion of unexpected lower results on two studies, the in vivo and the RBL.
The purpose of the testimony is to show that the findings reported in example 2A do not, in fact -- when you understand all the information, that information does not support a determination of unexpectedly lower results. In fact, you've got no death, no mouse death above the five to nine rage. So the test, when understood in full, doesn't

support unexpectedly lower results.

To the extent the RBL test might be used to support unexpectedly, this simply indicates that the RBL test is not viewed as a reliable indicator of toxicity.

So on both counts, the in vivo tests, four results are not in fact consistent of unexpected results. And in the RBL test, that test isn't a reliable indicator of toxicity that there is a failure of proof of unexpected results. That's the purpose of the testimony, your Honor.

MR. WIESEN: Your Honor, with that proffer, it's plain that the testimony is actually not relevant to the question of unexpected results, which, as a matter of law, are not limited to the data that's contained within the patent. Extensive data was entered into evidence at the first trial beyond what's in the patent, beyond what's in the April '94 data table. And if the testimony is going to be limited to only this subset, then it's legally irrelevant to the question of unexpected results.

THE COURT: He's not done yet. What else are you doing, Mr. Jones?

MR. JONES: We are just about finished, your Honor. She's going to talk about all that other data and whether that would affect the confidence of a toxicologist in a finding of unexpected results.

THE COURT: She is going to talk about it?

MR. JONES: Yes, of course.

THE COURT: Okay.

MR. JONES: Yes.

Q. All right. Going back to DTX-1256, this is a document prepared by Dr. Pinchasi in 2003, that you discussed in your expert report?

A. Yes, I did.

MR. JONES: I'll note for the Court that DTX-1256 has been admitted during the testimony of Dr. Pinchasi.

Q. Dr. Rice, would you please read into the record those parts of DTX-1256 that discuss relative utility of the RBL and in vivo tests as it pertains to toxicity?

MR. WIESEN: Your Honor, what Dr. Pinchasi did or didn't say is not relevant to the question of unexpected results. We've read this document many times before.

MR. JONES: It's simply she offered an opinion that the RBL did not show a good correlation with toxicity. You can't have confidence, you cannot have confidence in it in a toxicity determination. And this simply shows Teva agrees that you cannot -- it's not a good test, it does not have predictive clinical value and that the in vivo test, fully understood, is what you need for toxicity.

THE COURT: All right. Well, you can -- it's in evidence, you can argue it.

MR. JONES: Very well.

Q. Doctor, or Dr. Rice, given the issues that you've

identified with the tests used in the '808 patent, how would a person of ordinary skill define a test that could credibly analyze the relationship between molecular weight and toxicity?
A. In order to properly define the relationship between molecular weight and toxicity, a study would need to be designed where, first of all, the batches of copolymer-1 were controlled, such that the only difference in the batches was due to the molecular weight. This would eliminate the possibility of other possibly unidentified factors contributing to toxicity.

In addition, you would want to test all of the animals at the same time and have a placebo control. By doing that and examining all of the animals in whatever test you decided was appropriate, whatever toxicology battery you wanted to do, with everything being held constant, but for the change in molecular weight batches, you would be able to determine where differences lie, if, in fact, there are any differences in toxicity.
Q. All right. Given your definition or given the definition of a test demonstrate unexpectedly lower results, Dr. Rice, did you in fact as part of your work review a number of test values related to toxicity that Teva had conducted?
A. Yes, I did.
Q. And in all those tests, did you see any test -- did you see evidence of any test that met the criteria that you set forth

for the type of test that one could rely on to show unexpectedly lower results?

A. No, I did not identify any. There were data scattered over time and experiments where there were individual values shown in the mouse in vivo test. Maybe a couple of different batches would have been tested on a particular day, with varied results. But I saw no consistent consistency in the batches that were being tested in the formulations that were actually being tested, and certainly nothing that was comparing at one time batches below, in the five to nine range, and those greater than around ten.

Q. Dr. Rice, given the prior art that you discussed here today, '550, and more particularly the Bornstein study, and given your understanding of the two, the in vivo test that's described in this patent specification as augmented by the information about the in vivo test that's provided by 3149T, given that information, does that information -- would that information show a person of ordinary skill in toxicology that co-polymer-1, in any form, exhibits unexpectedly lower toxicity?

A. No.

Q. Why, why do you conclude that?

A. I conclude that because there's, essentially, no difference that has been shown in the toxicity of the batches or the copolymer compositions between five to nine kilodaltons, and

compositions ten and above.

MR. JONES: In fact, I have no further questions. Thank you, Dr. Rice.

THE COURT: All right, we're going to take a ten minute break.

MR. WIESEN: Thank you, your Honor.

(Recess)

(Continued on next page)

CROSS-EXAMINATION

BY MR. WIESEN:

Q. Good morning, Dr. Rice.

A. Good morning.

Q. We've met before at your depositions, correct?

A. Yes, we have.

Q. Dr. Rice -- we'll hand out some binders, your Honor, before we start. Dr. Rice, during your direct we heard some references to a trial we had in July. Do you recall that?

A. Yes, I do.

Q. You weren't here for that trial, right?

A. That's correct.

Q. Have you reviewed the transcripts that were taken in that trial?

A. I reviewed a couple.

Q. You're aware there was testimony in that trial concerning toxicity issues with copolymer-1?

A. Yes, primarily the RBL test.

Q. You're aware there was testimony concerning some of the documents that you put on during your direct today, correct?

A. Yes.

Q. Did you review the testimony from Dr. Pinchasi from Teva on those issues?

A. I believe I did.

Q. Did you review the testimony of Dr. Arnon from the Weizmann

Institute on those issues?
A. Yes, I did.
Q. And did you review the testimony of Dr. Barbara Baird from Cornell on those issues?
A. Yes, I did.
Q. Are you aware additional data in the RBL test was discussed during that trial?
A. I vaguely remember.
Q. You didn't talk about that additional data specifically today, right, Dr. Rice?
A. No, I did not.
Q. You talked briefly about or a little bit about the '550 patent. Do you recall that testimony?
A. Yes, I do.
Q. If you need it I think it's PTX 26 in your binder. You may not need it for these questions. We'll see if you do.

Now, you're not interpreting the molecular weight data in that document, correct?
A. No, not interpreting.
Q. You're just reading the numbers off the page basically, right?
A. Basically, and what I've been instructed, yes.
Q. And comparing the numbers in that document to the numbers on the page in another document, correct?
A. That's correct.

Q. You're not an expert in measuring molecular weights, right?
A. No, I'm not an expert.
Q. You don't know what different results you may or may not get depending on the methodology used to measure the molecular weight, right?
A. No, not specifically. I do know that you could get different numbers.
Q. You don't know what method was used to measure the molecular weight in the '550 patent, do you?
A. No.
Q. Do you know what method is used to measure the molecular weight in the patents in dispute in the '808 patent?
A. I don't remember if I did know.
Q. And you agree, Dr. Rice, that there's no data in the '550 patent concerning toxicity one way or the other, correct?
A. That is correct.
Q. So the '550 doesn't teach anything to a person of ordinary skill in the art about toxicity or lack of toxicity for copolymer-1, right?
A. That is correct.
Q. Dr. Rice, you talked a little bit about what a person of ordinary skill in the art would expect about toxicity in polymers of different weights, do you recall that?
A. That's correct.
Q. Now, do you agree with me, Dr. Rice, that a person would

not expect that lowering the molecular weight of a polymer would always decrease the toxicity, right?
A. Of course, no.
Q. They'd have no expectation one way or the other whether lowering the molecular weight might increase toxicity, decrease toxicity or leave it the same, right?
A. That's correct.
Q. So any change -- if there were a lowering of toxicity, if there were, that would be unexpected, correct? When you lower the molecular weight?
A. I don't -- I wouldn't characterize it as being unexpected because it's known that changing various parameters can affect toxicity profiles. So no, I wouldn't be surprised.
Q. Well, to be clear, what's known is that there can be a change in the toxicity profile when there is a change in molecular weight, right?
A. That's correct.
Q. But it's not known that there is always a relationship when you decrease molecular weight you decrease toxicity, right?
A. That's correct.
Q. Sometimes you decrease molecular weight and you increase toxicity, correct?
A. That's correct.
Q. And sometimes you decrease molecular weight and toxicity doesn't change at all?

A. That's correct.
Q. So there's no expectation ahead of time that when you decrease the molecular weight you will decrease the toxicity, right?
A. I have no expectation that a change would occur in a specific direction, but I wouldn't be surprised if it happened.
Q. Okay. Could you turn to DTX 1250, it's in your direct binder, please. It's also up on the screen, Dr. Rice. It's a short document, I think you'll recognize it. It's in your direct binder.
A. In the direct, I'm sorry. Yes, I see it.
Q. You testified about this document on direct, correct?
A. Yes, I did.
Q. Now, this document talks about safety, right? In the last paragraph?
A. Yes, the safety and chemical characteristics, yes.
Q. And you agree that reference to safety, I think you talked about it on direct, is in the context of regulatory agencies, right?
A. Yes.
Q. Do you agree that for regulatory agencies like the FDA safety is a risk benefit analysis, right?
A. Yes, it is.
Q. It's a balance between efficacy and side effects, correct?
A. That's correct.

Q. The FDA, for example, considers that balance between efficacy and side effects in whether to approve a drug, correct?
A. That's correct.
Q. And depending on the indication for a drug, some side effects are allowed for approval, right?
A. That's correct.
Q. Now, in the patents here we're talking about specifically toxicity, right?
A. Yes.
Q. And you agree there's a difference between how toxicity is used in the patent and how the term safety is used at regulatory agencies like the FDA, right?
A. That's correct.
Q. Let's talk about the RBL test for a minute. You provided some testimony concerning the RBL test in your direct, correct?
A. Yes, I did.
Q. You looked at that one column of RBL data on that April 1994 data table?
A. Yes.
Q. Now, Dr. Rice, before you got involved in this case, you thought you had heard of the RBL test, right?
A. Yes. I don't know specifically the RBL test, but I was familiar with degranulation tests.
Q. Right. Degranulation tests have been around for a while?

A. Yes, they have.
Q. And you agree that degranulation of human mast cells can be associated with certain adverse effects, right?
A. Yes.
Q. And in vitro degranulation tests are models for what might happen in vivo, right?
A. Yes.
Q. But you yourself before this case had never actually conducted an RBL degranulation assay, right?
A. No, not that particular cell type.
Q. You don't consider yourself to be an expert in the RBL degranulation test, right?
A. No, I do not.
Q. In fact, when you first started working on this case, you didn't even feel comfortable opining about the RBL test because you didn't have time to investigate it, right?
A. I didn't have time to investigate it, yes.
Q. And even today outside of the context of copolymer-1, outside the context of this case, you haven't looked at whether the RBL degranulation test is a reasonable model to measure potential undesirable local or systemic side effects, have you?
A. Correct, I have not independently investigated that.
Q. Did you read the testimony of Dr. Kimber from the July trial?
A. Yes, I did.

Q. And you understand that he was a witness brought by the defendants to testify about the RBL test?
A. Yes, I do.
Q. You think Dr. Kimber is more familiar with the RBL test than you are, right?
A. Yes. He has spent more time working on it in the context of his research and also copolymer-1.
Q. So he knows more generally and more in the specifics of this case about the RBL test than you do, right?
A. I would say he does.
Q. Now, you talked only about the RBL data that was in the April '94 data table during your direct specifically, correct?
A. That's correct.
Q. You'd agree with me that to talk about the overall toxicity in the RBL test, you need to look at all the data, right?
A. Yes.
Q. You can't just rely on some subset of data to reach a conclusion, right?
A. That's correct.
Q. And you know that Teva generated, Teva and the Weizmann Institute generated other data beyond what's in the April 1994 data table, correct?
A. Yes, and I've seen considerable other data.
Q. You don't know whether you've seen all of it, though, right?

A. No, I do not know for a fact I have seen all of it.
Q. But you know that more than you talked about specifically on direct was discussed during the April -- during the July trial, right?
A. Yes, it was.
MR. WIESEN: Mr. Chase, if we could have slide 44 from Dr. Baird's testimony in the July trial. And I believe this was actually marked as part of PTX 887, your Honor.
THE COURT: All right.
Q. Have you ever seen this slide before, Dr. Rice?
A. It looks somewhat familiar, but I can't say for sure I've seen it before.
Q. Did you look at the exhibits that were used at the July trial?
A. No, I did not see the exhibits.
Q. Did you look at the demonstratives that were used at the July trial?
A. No, I did not see them.
Q. Well, let me represent to you that this was a demonstrative that was used by Dr. Baird whose testimony I believe you said you read, correct?
A. I'm sorry, did you say Dr. Baird?
Q. Yes.
A. That's fine.
Q. Do you see at the bottom here it says average molecular

weight in daltons?
A. Yes, I do.
Q. Up on the Y axis it says percent degranulation?
A. Yes.
Q. And there's three exhibits noted in the bottom left-hand corner, PTX 1, DTX 3149T and PTX 34?
A. Yes, I see those.
Q. And you haven't reviewed the data that Dr. Baird has graphed on this demonstrative, correct?
A. Not knowing -- I would have to look at the individual --
Q. I'll withdraw that.
A. I did not specifically review these, no. That was not my intent.
Q. And you didn't testify about all of this data during your direct examination, correct?
A. No, I did not.
Q. Dr. Baird -- I'm sorry, Dr. Rice, you spent a little bit of time talking about the different batches and the different ways they were made?
A. Yes.
Q. How are the marker batches different than the final product batches?
A. I do not know for a fact how they are different.
Q. You just understand there's some difference.
A. From Dr. Gad's testimony, I understand that there is a

difference.
Q. Was the type of difference important to you in your analysis?
A. It would be important for me to know what the difference was, but as I mentioned earlier, to make a good comparison one would need the batches to be prepared in the same way and then the comparison in the animal test to be done at the same time instead of at various times across years and years.
Q. So it would be important for you to know what the difference is between the marker batches and the final batches, but you didn't investigate that question in giving your testimony here today?
A. I tried -- I tried to find out, but I could not, I did not find out for sure what the differences were.
Q. You talked a little bit about the Bornstein paper during your direct examination. Do you recall that?
A. Yes, I did.
Q. The Bornstein paper was before the Patent Office during the prosecution of these patents, right?
MR. JONES: Objection, foundation.
MR. WIESEN: I'll rephrase.
Q. The Bornstein patent is cited in the specification; we saw that during your direct, right?
MR. JONES: Your Honor, foundation. This is actually an area of patent law. Because it's important how -- one

minute counsel, please. When a paper is simply cited in the specification the paper itself is not necessarily given to the PTO. The record here is fairly clear that the Bornstein '87 study was not actually given to the PTO until the 2004 IDS, ten years after the patents were applied for in 1994. So a stray citation of a paper in the specification does not in fact mean that that paper was physically in front of the PTO, and it's apt here because the citation of Bornstein in the '808 spec pertains to the effectiveness of the drug. It does not appear in the toxicity section.

THE COURT: All right. Mr. Jones, I'm going to allow the question. Go ahead, Mr. Wiesen.

Q. You know the Bornstein paper is cited in the first column of PTX 1, right?

A. Yes.

Q. You know at some point during the prosecution as your counsel just represented that an actual copy was given to the Patent Office, right?

A. Yes, it sounds like.

Q. And even with the Bornstein paper in front of the Patent Office, they allowed these patents to issue, right?

MR. JONES: Objection. Relevance.

THE COURT: It doesn't matter. It's a matter of record one way or the other. You don't need to answer. Next question.

Q. I want to turn just briefly to the in vivo toxicity results you testified about.
A. Yes.
Q. All toxicologists generally should be familiar with this test, right?
A. Most are, yes.
Q. It's a fairly standard test for acute toxicity?
A. It's one of a number that are used, yes.
Q. It's similar to a test that's in the United States Pharmocopeia, right?
A. Yes, it is.
Q. Now, for this test as well you talked only about the data specifically in the April '94 data table, right?
A. That is correct.
Q. And you're aware that Teva also generated additional data in this in vivo toxicity test, right?
A. Yes, I am aware there is additional data.
Q. And like the RBL data, you don't know whether you've seen all the data that was generated by Teva and the Weizmann Institute, right?
A. I believe I have seen all of the data that was available. I've sat down with counsel and searched a database of the Teva documents provided to actually look at those and to identify them.
Q. You've done that since your deposition, Dr. Rice?

A. No, actually, it was before my deposition.
Q. So before your deposition you had reviewed the documents and you were sure you'd seen all of the data?
MR. JONES: Objection.
A. At the time of my deposition I wasn't sure that there wasn't more information that was out there and available and that we hadn't seen. Since my deposition, I've been told that everything that was available -- that essentially there wasn't anything more available for me to look at, so I had seen everything that was available.
Q. And the --
MS. BLOODWORTH: If I could object, your Honor. This is the same issue we had with Dr. Baird in the July trial about whether or not Teva provided all the data underlying example 2. We had apparently a miscommunication or a misinterpretation of the magistrate judge's order and I think we came to the resolution with Dr. Baird that the witness was under the impression that we had produced all the data that Teva provided to us.
THE COURT: I'm still confused. Why don't we finish with the witness, then we can discuss it.
MS. BLOODWORTH: Thank you, your Honor.
Q. During your direct examination you didn't talk about all the data in the in vivo toxicity tests that you had seen, right?

A. No, I did not talk about all the data.
Q. And you agree that in Teva and Weizmann Institute's data there are batches between 10 and 15,000 daltons that were toxic in the in vivo toxicity test right?
A. There were some that were toxic, and there were some that were toxic at lower ranges.
Q. If you could turn to page PTX 34T in your exhibit binder. You reviewed this document in rendering your opinions in this case?
A. Yes, I did.
Q. If we look at the first table on this page the second batch down, 24P1, do you see that?
A. Yes I do.
Q. It reports a molecular weight of 14,000 daltons, correct?
A. That's correct.
Q. And that's toxic in the in vivo test, right?
A. Yes, it is.
Q. If we go down to the next table, you see batch 54019? Fourth line down?
A. Yes, I see it.
Q. That reports a molecular weight of 15,600 daltons, right?
A. That's correct.
Q. And that's toxic in the in vivo test, right?
A. That's correct.
Q. Could you turn to the next page, the second table down, the

fifth entry, batch 27I8, do you see that?
A. Yes, I do.
Q. That reports a molecular weight of 12,400 daltons, right?
A. Yes, it does.
Q. And that's toxic in the in vivo test, correct?
A. Yes, it is.
Q. Turn to the next page. We're almost done with this document. If you highlight that table at the top. Here the second line down has a molecular weight of 9,000 daltons, right?
A. That's correct.
Q. And that's one that's toxic in the in vivo test, correct?
A. Yes.
Q. And then right below that are two batches that are 11,000 daltons, correct?
A. That's correct.
Q. And those are both toxic in the in vivo test, correct?
A. Yes.
Q. You haven't done any statistical comparison at all of the toxicity of batches above 10,000 and between 5 and 9,000 daltons in the in vivo toxicity test, have you?
A. No, and I wouldn't do it because it's inappropriate to do so. The batches are not prepared in the same way, they were not examined at the same time, so it is inappropriate to do any kind of statistical analysis.

Q. Dr. Rice, you haven't even counted the number of batches above 10,000 that are toxic in the in vivo test, have you, in the Teva data and the Weizmann data?
A. I didn't specifically count it, but I certainly did look at the information.
Q. And you didn't calculate the percentage even above 10,000 that are toxic versus the percentage between 5 and 9,000 daltons that are toxic, right?
A. No, because I view it as being irrelevant.
MR. WIESEN: I have no further questions, your Honor.
THE COURT: All right.
MR. JONES: Very brief redirect, your Honor.
REDIRECT EXAMINATION
BY MR. JONES:
Q. Dr. Rice, is Dr. Pinchasi a toxicologist, a person of skill in the art in toxicology?
A. Not that I remember.
Q. Is Dr. Baird a toxicologist?
A. No.
Q. Is Dr. Arnon a toxicologist?
A. No.
Q. Would any of those three people, would they qualify as a person of ordinary skill in the art of toxicology, with a PhD in toxicology or related field and three to four years practical experience?

A. No, they would not.
Q. So the Baird chart that you were shown is prepared by someone who is not a person of ordinary skill in the art, is that your understanding?
A. Yes, that's my understanding.
Q. Doctor, you understand that the issue that you were asked to talk about, to testify about was unexpectedly lower results, correct?
A. That's correct.
Q. You testified about the Bornstein 1987 study, correct?
A. That's correct.
Q. And just so we're clear, that Bornstein study had copolymer-1 of 14,000 to 23,000 daltons, correct?
A. That's correct.
Q. Now, what was the toxicity of that batch, of those batches of copolymer-1 used over a two-year period?
A. There was no evidence in the patients administered the copolymer-1 that there was any significant toxicity.
Q. No toxicity in 14,000 to 23,000?
A. That's correct.
Q. As a toxicologist, can you show unexpectedly lower results than no toxicity?
A. No, you can't.
MR. JONES: No further questions.
THE COURT: All right. Anything else?

MR. WIESEN: Nothing, your Honor.

THE COURT: All right, thank you, Dr. Rice, you may step down.

(Witness excused)

THE COURT: Next witness?

MS. HAGBERG: Your Honor I believe it's our turn now on behalf of Sandoz, Momenta, and we will call Dr. John Bishop. He's out in the hall. May we have a moment?

THE COURT: Yes.

(Pause)

JOHN BISHOP,

called as a witness by the Defendant,

having been duly sworn, testified as follows:

THE COURT: Please take your seat. Tell us your full name and spell your last name.

THE WITNESS: Yes. My name is John Edward Bishop, B-i-s-h-o-p.

DIRECT EXAMINATION

BY MS. HAGBERG:

Q. Good morning, Dr. Bishop.

A. Good morning.

Q. Would you like a bottle of water? It's going to be a little while this morning.

A. That would be helpful, please.

Q. May I ask by whom you are employed?

A. Yes. I'm employed by Momenta Pharmaceuticals.
Q. Where is Momenta located?
A. In Cambridge, Massachusetts.
Q. And what is your current position?
A. Senior vice president pharmaceutical sciences.
Q. And in that position what are your responsibilities?
A. My responsibilities are broadly for the what we call the CMC, or chemistry manufacturing and controls section of our drug development programs.
Q. And can you just tell the Court generally what falls within the CME organization?
A. CMC.
Q. CMC, excuse me.
A. It consists of process development for the active ingredient or the drug substance, process development for the drug product, quality control and quality assurance.
Q. And what is your educational background, Dr. Bishop?
A. I have a bachelor's degree from Tufts University in chemistry and a PhD in organic chemistry from the University of California Berkeley.
Q. So turning to Momenta, what is Momenta's business?
A. We are a biotechnology company. We were an outgrowth of several professors' laboratories from MIT where we took some proprietary technology from those professors' laboratories and formed a company based on that.

Q. And when was the company founded?
A. Approximately ten years ago. The early 2000's.
Q. And does it have a particular business plan as a small company, market plan?
A. Yes, our business plan is to apply these analytical technologies from the MIT labs originally to drug development programs.
Q. Just generally what kind of analytic technologies are you referring to?
A. These are analytical technologies, again, proprietary technologies that are designed to give a high level of resolution, high level of analytical resolution to the class of drugs that we call complex mixture drugs.
Q. And how many employees does Momenta currently have?
A. We currently have about 190 employees.
Q. So when did you first join Momenta? And I apologize if I asked you that already.
A. I joined in I believe it was the fourth quarter of 2004.
Q. And what was your position at the time that you joined Momenta?
A. My title was vice president pharmaceutical sciences.
Q. And what were your duties and responsibilities at that time?
A. Pretty much the same as they are now, however, with a much smaller group at the time. I was really charged with

responsibility of starting up the chemical development program at Momenta. It was a very young company at the time and primarily had been oriented to research. So when I was hired, I was hired to start up the development aspect of the pharmaceutical development programs.

Q. Who do you report to in your current position as vice president for pharmaceutical sciences?

A. I report to our chief executive officer, Craig Wheeler.

Q. And other than your title as senior vice president, do you hold any other positions at Momenta?

A. Yes. I'm also a member of the executive committee of the company.

Q. And what does the executive committee do within Momenta?

A. We manage the company. It's basically the corporate functions within the company.

Q. You mentioned that Momenta's business was focused on complex drugs. Could you explain for the Court what you mean?

A. Yes. Most drugs consist of one active ingredient. Just a simple example would be aspirin, where the active ingredient is one molecule, acetylsalicylic acid. Most drugs similarly have just one active ingredient. We've chosen at Momenta not to be in that realm of what's called small molecule drugs, but to apply our proprietary technologies to these complex drugs and that is drugs that have more than one active ingredient associated with them. Generally speaking, many, a collection

of many active ingredients.
Q. And what challenges, if any, do complex drugs pose in comparison to drugs with a single active compound in terms of developing and manufacturing them?
A. I would say what distinguishes the complex drugs is the ability to properly characterize them, certainly for the purposes of getting approval by the FDA. Small molecule drugs or single active ingredient drugs are relatively easy to characterize and control using modern analytical technologies. That's because they just have one type of molecule associated with it. A complex mixture drug can have hundreds, if not thousands of active ingredients or molecules associated with the active ingredient and therefore pose very difficult chemical analytical challenges.
Q. Has Momenta since its founding successfully developed any what you've been referring to as a complex drug?
A. Yes, we have.
Q. Can you give me an example?
A. Yes. About a year ago we received approval for a drug called the Enoxaparin sodium, which is very much so a complex drug.
Q. And was there a team working on developing that drug in addition to you?
A. On which drug?
Q. Enoxaparin.

A. Yes.
Q. Can you tell the Court very briefly the kind of development you went through in developing Enoxaparin?
A. Yes, we would go through -- the early stages preceded my employment at Momenta, but the very early phase was a research phase which was really geared towards further developing and implementing those analytical technologies in order to understand the drug that was on the market. The parent drug is called Lovenox and taking that information and reverse engineering the manufacturing process in order to make a drug that we could prove to the FDA's satisfaction is equivalent in all of those chemical components to what the marketed drug is.
Q. Are you familiar with the drug Copaxone?
A. Yes, I am.
Q. And you understand that this trial today relates to that drug and patents relating to that drug?
A. Yes, I do.
Q. Do you consider Copaxone to be a complex drug?
A. Yes, I do.
Q. Why is that?
A. Because it consists of more than one active ingredient, in this case many more than one molecule constitute this mixture.
Q. And what is glatiramer acetate?
A. Glatiramer acetate as I understand it is the name that's given to the active ingredient in what is called Copaxone.

Q. Did there come a time when Momenta became interested in developing a form of drug with glatiramer acetate?
A. Yes.
Q. And when did Momenta first become interested in that drug?
A. I would say the initial interest was in the late 2004, early 2005 time frame.
Q. And was there any particular reason why that drug was of interest to Momenta?
A. Yes. It was brought to our attention by a couple of members of our board of directors and our founders from the MIT faculty with a feeling that the complexity of this drug fit very nicely into the niche of complex drugs in which we were working, and therefore would be a logical second program for us to work on in addition to the program I mentioned earlier, Enoxaparin.
Q. Were you involved in the decision of whether to pursue development of a generic glatiramer acetate?
A. Yes, I was.
Q. And what steps did the company take as part of its assessment, preliminary assessment of whether to proceed?
A. Well, the first steps were to form just a small I think we called it an ad hoc team at the beginning of scientists to evaluate what was known about this drug, and from that evaluation make a recommendation as to whether to proceed with a program or not.

Q. And just very briefly, do you recall who the team members were at the time?
A. Roughly I do, yes.
Q. And who were they?
A. It would be myself, my counterpart in research, Ganesh Venkataraman and several members from our analytical group, Zach Schreiber and Corrine Bauer. I think there may have been a couple of other scientists involved, but that was the core of the team.
Q. And do each of those team members have an advanced degree in the relevant technology for the development of Copaxone or relating to Copaxone?
A. Yes, very much so.
Q. So what was the first step that this team did in order to make an assessment of whether to proceed with a generic form of glatiramer acetate?
A. Well, I think the members of the team had not heard of this drug before, and so the first thing we wanted to do was acquaint ourselves with what we could find in the literature related to this drug.
Q. And is that typically what you would do or is that what you did with Enoxaparin?
A. Yes.
Q. What did the team find as a result of its literature study?
A. Well, we found some things in the literature related to

this drug. We requested and received a literature search and got several publications, articles, etc., related to this drug.

Q. Can I -- just because you've not been here since the trial began, the way we are proceeding is that there is a binder with copies of exhibits that I intend to ask you about at least some of those in front of you, and could I ask you, please, to turn to Defendant's Exhibit, it's marked DTX 1074, please.

THE COURT: And as we go along, you'll also find it on the screen.

THE WITNESS: I just saw it. Thank you.

Q. You could look either place if it's easier to focus.

A. Okay.

Q. Have you seen this document before?

A. Yes, I have.

Q. What do you understand it to be?

A. I understand this to be the package insert for Copaxone.

Q. And was this one of the documents that came up as a result of this search that you had initiated, your team had initiated at Momenta?

A. Yes. It's one of the hits from our literature search.

Q. Can I ask you now to look at DTX 3563 in your binder? And again, it's up on the screen, Dr. Bishop.

A. Yes, I see this.

Q. And do you know what that document is?

A. Yes, I do.

Q. And what is that document?
A. I recognize this as the label of Copaxone.
Q. And was this one of the documents that was turned over as part of the study that you had performed?
A. Yes.
MS. HAGBERG: Your Honor, I'd like to move for admission Defendant's Trial Exhibit 1074, the package insert and also the Copaxone original label, DTX 3563.
THE COURT: First one might be in evidence already, but in any event, is there any objection?
MR. HASHMALL: It's a different version, but no objection, your Honor.
THE COURT: All right. They are both admitted.
(Defendant's Exhibits DTX 1074 and DTX 3563 received in evidence)
Q. If I could ask you to turn back now to Defendant's Exhibit 1074, Dr. Bishop, what if anything did your team learn from Exhibit 1074, which is a package insert from the marketed drug Copaxone?
A. Well, we learned basic information about the drug. We learned what the four amino acids were that comprise the copolymer. We learned the average mole fraction of those four amino acids, and we learned the average molecular weight of glatiramer acetate, that's also indicated on this label.
Q. And just so there's no confusion, did you at some point

later in time become aware of a revised or a different version of the Copaxone product insert?
A. Yes, we did.
Q. And was there -- and let me highlight and show that document, which I believe was put into evidence as Plaintiff's Trial Exhibit 697. Is Plaintiff's Trial Exhibit 697 a document you've seen before?
A. Yes, it is.
Q. What if anything further did your team learn from Plaintiff's Exhibit 697?
A. Well, we learned that this is a revised package insert for the drug and in this revised package insert there was a change to the molecular weight range indicated for the product.
Q. So in addition to package insert and the drug label, were there any other materials that were identified to you and your team that were -- that you considered in your early stages of your development of generic glatiramer acetate?
A. Yes, there were other sources.
Q. And what kinds of documents did you look at?
A. Well, in general this first class that we just looked at I would say fell into the class of regulatory documents that we looked at. Two additional classes of documents would be literature, literature articles and a second class would be generally patents, and patent applications.
Q. And in terms of, let's deal first with literature articles,

is there anything that you recall from your early study that gave you any information about Copaxone?
A. Yes. There was.
Q. And what was that?
A. I remember some articles from the very early 1970's related to this drug.
Q. And I'd like to ask you to turn in your binder to Plaintiff's Trial Exhibit 499, and I'm sorry, your Honor, to put this up one more time.
THE COURT: Okay.
Q. Mr. Bishop -- well, once you've gotten to that page -- that was 499.
A. I could just follow it on screen. That might be easier.
Q. All right. Is that the article that you were referring to, Mr. Bishop?
A. Yes. This is a 1971 article from the European Journal of Immunology.
Q. And we've been -- this is not the first that the Court is seeing this exhibit and it's being referred to as the Teitelbaum article. Is it okay with you if I refer to it that way?
A. Yes.
Q. What disclosure did the Teitelbaum journal make to you and your team with respect to copolymer-1, if any?
A. If we can flip, or just stay on -- yes.

Q. Go ahead.
A. So in Section 2.3.1 it disclosed a basic synthetic root for the drug, namely of three reaction steps; polymerization, depolymerization and deprotection.
Q. And was there anything else in this article that you considered relevant to your study? And may I refer you to table 1, just to --
A. Yes, in table 1 it disclosed I believe it was two, yes, two batches of material that were made by that synthetic methodology described earlier. It basically gives results. This table gives results for two different batches indicating the amount of the amino acids charged or added into the first step as well as the amino acid ratios of the product produced at the end.
Q. And just, can you explain to the Court when you say "charged," what's the difference between the charged amount and the end amount?
MR. HASHMALL: Your Honor, just an objection. I mean, this is a fact witness, obviously. To the extent that the testimony is sort of leaning towards what information would be disclosed in these prior art disclosures, I'm concerned we're getting into expert testimony rather than fact testimony.
THE COURT: All right. I'll be sure to take note of that.
THE WITNESS: I'm sorry, what was the question again?

THE COURT: I don't suppose there's a lot more of this.

MS. HAGBERG: There's not, your Honor.

Q. The question was, you referred to a charged amount and then an amount in the product. What did you mean by that?

A. By the amount charged I'm looking at the column amount used in the reaction and to me that means the amount of the amino acids that are added into what we call step 1 of the process or the polymerization reaction in the process.

Q. And then what were you referring to in the batch 1 and batch 2 columns?

A. So the last two columns indicate to me the amino acid ratio of two batches of this copolymer-1 which were produced by this process.

Q. Thank you, Mr. Bishop. And I think you mentioned a third class of materials. What was the other group of materials that you looked at?

A. That would be patents and patent applications.

Q. And which patents if any did your team find during this time period? Just to be clear, roughly what time period are we talking about?

A. This would be in the early 2005 time period.

Q. And so my question was what patents, if any, did you find that related to your study of Copaxone?

A. I recall several patents that basically gave similar

information to what was described in this article that we just saw.

Q. And do you remember anything specifically from -- well, let me back up and ask you a more basic question. Do you remember seeing the '808 patent which is one of the patents in suit in this case?

A. I haven't memorized the patent numbers.

Q. You're welcome to look at it. It's PTX 1, and maybe I will ask -- it's in your binder, so we don't -- it's up on the screen, too, and ask you, that is one of the patents that you saw?

A. Yes, I recognize this.

Q. What if anything -- you can take that down, please. What if anything did you learn from the '808 patent about copolymer-1?

A. I recall this reiterated much of the same basic information that was given in that earlier journal article that we just saw, and I recall that the molecular weight, the reported molecular weight for the material had changed.

Q. And do you remember what the molecular weight is that is reported in the patent? If we put the patent back up on the screen, maybe we can help you.

A. Yes. What's indicated in this patent is a -- I believe it shows a molecular weight of 7,000 plus or minus 2,000 daltons.

Q. And just so we can see that on the screen, could you put up

column 4, line 55 to 65? And was there any other information that you observed in the '808 patent about copolymer-1 that you believe was relevant?

A. Again, it reiterated what was reported in the earlier literature for this compound.

Q. Did it tell you how the molecular distribution of the two batches was determined?

MR. HASHMALL: Your Honor, I'm going to object to this. I don't understand the relevance of this testimony. Obviously, Mr. Bishop is a fact witness, he's not being qualified as a person of ordinary skill in the art, which is I think the issue to be resolved in this phase of the trial, so I'm not -- what Mr. Bishop learned or deduced from these patents, I don't understand it.

THE COURT: What is the purpose of this testimony?

MS. HAGBERG: Actually, your Honor, I submit that Dr. Anderson and his group do qualify as one of ordinary skill in the art, and he fits Teva's definition of ordinary skill in the art, he will fit into the definition of ordinary skill in the art that our witnesses are going to describe, and yes, he is here as a fact witness, he is not here as an expert, but his testimony regarding how Momenta developed the product and what their product is and incorporates and the issues that they raise we believe is relevant both to our invalidity and our non-infringement defenses.

MR. HASHMALL: I think I just heard Ms. Hagberg suggest that he is an expert he's going to give what the Court should consider as expert testimony. As I understand the Federal Rules, we should have been given an expert report. If he's not been qualified as an expert, the Court can't accept him as an expert, I have heard no testimony about his knowledge of SEC, measurements, molecular weights, all the questions that other experts have been asked. He's a fact witness. We have lots of experts we're going to be hearing from on this issue, I don't understand how this testimony could be admitted.

THE COURT: I really don't mind if Dr. Bishop wants to talk about his background with Sandoz in general strokes, but he shouldn't be testifying about the chemistry and what it means.

MS. HAGBERG: Your Honor, he's not going to be giving expert testimony. I'm not going to ask him any legal conclusions based on any of the work that was done by Sandoz and Momenta. It's only the factual story of what Momenta did and what its product, what its resulting product, the characteristics of its resulting product, and if you'll allow me, your Honor, to continue, and Mr. Hashmall has -- I can take this down, he said what he wanted to say about this patent, I have nothing further on this.

MR. HASHMALL: I have no objections to hearing about the characteristics of the product, but as to what he was

learning about the prior art, I do have an objection.

THE COURT: Are you done with this?

MS. HAGBERG: I'm done with this, your Honor. I tried not to put it up here, if I could.

Q. So after you had done the art study, what did you do next?

A. Well, the next step was, we realized that this body of literature didn't really give us the kind of information, it gave us some very basic information about the drug, but it didn't give us anywhere near enough information in order to produce a package that we would eventually be able to take to the FDA.

MR. HASHMALL: Your Honor, I'm reluctant to stand up, but I move to strike the testimony.

MS. HAGBERG: Your Honor, this is the story of what they did and what they encountered in getting to their product.

THE COURT: Move it along. I understand the inference you're concerned that one might draw from the last statement, but let's keep moving. Okay.

Q. Did you do any work with the actual product?

A. Well, that became the center point of our overall development effort. We realized that the information that we could get from this was rather limited with respect to the package that we would eventually need to file, and so we turned our attention to extensive analysis of the marketed drug, that is, the drug that we could purchase from the market and subject

to our methods of analytical chemistry.
Q. And just so the record is clear, you said the package that you would need to file. What do you mean by that?
A. The package that we would need to file eventually for registration and hopefully eventual approval with the FDA.
Q. And about again, just to keep this in a time frame, what time are we speaking about now that you were referring to?
A. This would be early in 2005.
Q. Did there come a time when Momenta began looking for a partner to partner with to develop generic glatiramer acetate?
A. Yes.
Q. And what potential partners did you speak to?
A. We spoke to really two types of companies. One would be companies in the generic drug space and the other would be pharmaceutical companies or novel pharmaceutical companies that had experience in the multiple sclerosis area.
MS. HAGBERG: Could you hold on just a moment, please?
(Pause)
Q. Who did Momenta eventually partner with?
A. We eventually partnered with Sandoz.
Q. And why did you choose Sandoz?
A. Well, primarily because we had an excellent existing relationship with Sandoz on our other program, Enoxaparin.
Q. And did Sandoz perform any due diligence on Momenta before it decided to partner with you?

A. Yes, they did.
Q. And were you involved with the due diligence in any way?
A. Yes, I was.
Q. As a result of your involvement, did you have any understanding regarding Sandoz' previous efforts to develop glatiramer acetate?
MS. HAGBERG: One question.
MR. HASHMALL: One question all right.
A. Yes, I learned that Sandoz had a prior effort in this area and had abandoned it.
Q. So when did Momenta begin collaborating with Sandoz to develop a generic version of Copaxone?
A. I would estimate the middle of 2006.
Q. Does Sandoz Momenta have a name for the product that is under development?
A. Yes, we do. That's a code name M356.
Q. So is it okay with you if I refer to that? It's a little easier for me to say than glatiramer acetate.
A. Yes, please.
Q. And how does Sandoz and Momenta divide responsibilities and oversight for the development of M356? And I'm primarily interested in who is doing the development work right now.
A. Momenta has responsibility for all of the research and development activities, and Sandoz has responsibility for commercial activities associate with the drug.

Q. And to date, how long has Momenta been working on development of M356?
A. This is about six years, now.
Q. And what's the team look like that is working on it today?
A. It's a group of about 40 to 50 scientists at Momenta.
Q. And to date, approximately how much has Momenta spent on development?
A. We've spent in excess of $50 million so far.
Q. And in your experience, is this a long time and a significant expense in the developing of a generic product?
MR. HASHMALL: Objection, your Honor. I don't see any relevance to this question.
MS. HAGBERG: I'll move on, your Honor, it's not --
THE COURT: Okay.
Q. What are some of the problems that you've encountered that has taken the time that it's taken?
A. Well, it's the inherent problem of characterizing a complex drug. It takes time, sophisticated methods and putting a package of that complexity together for the FDA is very challenging.
Q. And what in particular do you have to match that was causing problems with you?
A. We have to match every aspect of the marketed drug and we have to prove that match to the satisfaction of the FDA.
Q. So turning to the molecular weight, I'd like to talk about

Momenta's efforts to determine the molecular weight of Copaxone. Can you explain generally what, or walk us through Momenta's efforts to measure the molecular weight of Copaxone? Does -- I think we have a demonstrative that you assisted in preparing regarding the evolution of their methods. Could I ask that Bishop 5 be put on the screen?

So what was the first method that Momenta or effort that Momenta made in trying to determine molecular weight? And first tell me, could you just describe what it was you were trying to determine and why.

A. Well, we were trying to determine the molecular weight of the marketed drug. The information that we had read from the various points of literature appeared to give conflicting information and ambiguous information with respect to what the molecular weight of the drug actually is. So we elected to charge through that simply by measuring the molecular weight in our laboratories. And we started with the methodology that's shown on this demonstrative, a technique called SEC MALS.

Q. Why did Momenta choose SEC MALS? First of all what is SEC MALS what does that stand for?

A. Size exclusion chromatography multi-angle light scattering.

Q. Why did Momenta choose SEC MALS as the first method to measure molecular weight?

A. We selected this method because it was an existing method within our company. We in our area of complex drugs we have

occasion to measure the molecular weight of all of our polymer drugs, so this is an existing standard 21st century method for measuring molecular weight. We used it for one of our other drug development programs successfully, and so we started with this methodology.

Q. And what is DNDC and 1 and 2?

A. So DNDC is one of the components that go into the output of the SEC MALS measurement, and we were at the beginning deriving or DNDC value for this technique from literature values.

Q. And what were the results of your use of SEC MALS trying to determine, and you were working from marketed Copaxone in trying to determine molecular weight, is that correct?

A. Yes. So for marketed Copaxone using this technique, we observed molecular weights, much to our surprise, that were far greater than what was on the package insert of the drug.

Q. Did Momenta keep records of its effort to use SEC MALS to measure molecular weight?

A. Yes, we did.

Q. And were those records kept in the ordinary course of its development work on M356?

A. Yes.

Q. Would you turn to PTX 198R in your binder, Mr. Bishop?

MS. HAGBERG: And, your Honor, this is a redacted document, I believe counsel has provided your Honor with the full non-redacted version.

THE COURT: Yes.

A. Yes, I see this document.

Q. And have you seen this document before?

A. Yes, I have.

Q. And what is it?

A. This is a technical report or an analytical method development report from our analytical development group.

MS. HAGBERG: Your Honor, we offer PTX 198 into evidence and, again, the public version is the redacted 198R.

MR. HASHMALL: No objection, your Honor.

THE COURT: Okay. Admitted.

(Plaintiff's Exhibit PTX 198 received in evidence)

Q. And what does PTX 198 show about the results of Momenta's 2005 SEC MALS measurement? I'd like to refer you to Section 6.2 on the first page.

A. Well, it's shown by this first DNDC measurement that the molecular weight of the marketed Copaxone samples that we measured was greater than what we expected it to be. And that's further shown on table 2. A couple of pages later.

MS. HAGBERG: Mr. Gueverra, could you please put up table 2 on the screen?

Q. And when you say it was higher, could you explain what you mean with reference to this chart?

A. Yes. So looking at table 2 in the first column this shows -- and we analyze 10, 15 lots of the reference listed

drug, that's commercial Copaxone that we bought from the market and the 1, 2, 3 columns that follow are the three columns that show the observed molecular weight using this SEC MALS methods.

Q. By RLD lot number, what does that refer to?

A. That refers to the lot number that's on the sample of material that we purchased.

Q. And RLD would be what?

A. Reference listed drug.

Q. And is that Copaxone?

A. That is marketed Copaxone, yes.

Q. And you show three different -- well, let me ask this in a different way. What does the Mn, Mw and Mp columns show?

A. These are the three sort of standard outputs of molecular weight measurement, Mn is number average molecular weight, Mw is weight average molecular weight and Mp peak average molecular weight. The following column, PD, is polydiversity.

(Continued next page)

BY MS. HAGBERG:

Q. And were you -- why were you using three different methods to measure?

MR. HASHMALL: Your Honor, I object. Again, I thought the understanding was we were just going to go a summary of the development

THE COURT: This doesn't sound like a summary. And if you're offering this for the truth of the results, this is not going -- I mean, are we having a summary of, in general terms? This isn't general to me.

Q. Could you summarize, in general, what you found as a result of the tests that are shown in plaintiff's trial Exhibit 198?

A. Yes. We found that by whatever method of measurement, whether it's Mm, Mw, Mp, that we were getting values for molecular weight that were greater than the label claim that we saw in the drug.

Q. And why was that a problem?

A. Well, it was a problem because we needed to try to reconcile that body of knowledge with, and explain that eventually, that discrepancy to the FDA.

MS. HAGBERG: Could you go back to slide five.

Q. What was the next -- so what did you do next?

A. Next, we tried to further optimize the SEC MALLS method by, instead of using some literature values for this DNDC value, we did some work to try to derive an actual DNDC value, and to

further refine the SEC MALLS methodology based on that.
Q. And what were the results of your use of GPCRI methods?
A. The results are given in that same table two that we saw earlier and, in general, the results were closer to the stated label range, but still high.
Q. And so what did you do as your next step in trying to match the Copaxone molecular weight?
A. The next step was to try to implement a methodology that we used for another one of our products, for the enoxaparin product, and that is to use GPC.

In the case of enoxaparin, we use heparin standards.

In the case of this drug, we wanted to look at protein standards.
Q. Would you please turn to defendant's trial exhibit 1685 in your binder.

MS. HAGBERG: And I believe, your Honor, this is already in evidence.
Q. Was there a -- excuse me.
A. Okay, I see that.
Q. And did you become -- could you tell tell me what this document is?
A. Yes. So this is a patent that we became aware of, I'd estimate in the, somewhere maybe in 2005, maybe early 2006 timeframe.
Q. And did that inform your decision of what type of method to

use to measure molecular weight?
A. Well, this described a methodology somewhat similar to that GPC protein standard methodology, except instead of using protein standards, using polypeptide standards.
Q. And do you know this as the Gad patent, Mr. Bishop?
A. Yes, I do.
Q. And did you attempt to make measurements using the polypeptide standards at some point in time?
A. Yes, we did.
Q. And what was the results of using those standards?
A. When we implemented the standards as described in this patent, we were able to get values for the drug only by looking at Np. That made sense with respect to that label claim of the drug.
Q. And could you please look at plaintiff's trial Exhibit 236 in your binder, please?
A. Yes.
Q. And have you seen this document before?
A. Yes, I have.
Q. And what is plaintiff's trial Exhibit 236?
A. This is a technical report, an analytical method of development report from our laboratories.
Q. Would that report be part of the development records that Momenta would keep as in the course of its development of M356?
A. Yes.

MS. HAGBERG: Your Honor, we offer PTX-236 into evidence.

MR. HASHMALL: I object, your Honor.

THE COURT: I mean, it's a business record, but other than the fact that it exists, I can't do anything with it.

MS. HAGBERG: Your Honor, it's relevant to the question of what the progress of the product and how the product that is currently reflected in the ANDA.

THE COURT: I'm just saying that no one -- I don't know whether I -- they're probably not going to get up on and cross on any of this, because he's not an expert, right, in terms of results. That's all I'm talking about. If all this is to tell me their efforts and what they think they found and the next step, fine.

MS. HAGBERG: That's exactly what --

THE COURT: Is someone else going get up and testify as an expert in this case?

MS. HAGBERG: Yes, your Honor. We're not trying to make him an expert witness.

MR. HASHMALL: I don't think there is an expert that's relying on these documents to offer an expert opinion in this case unless -- correct me if I'm wrong, but I'm not aware of it.

MS. HAGBERG: Your Honor, this is just their development story. I'm going to ask him one question on this

document and then I will move on.

THE COURT: All right, well, I don't really need the document, I mean, except to --

MS. HAGBERG: That's fine?

THE COURT: Okay, let's go.

MS. HAGBERG: We can ask him the question?

THE COURT: Let's just hear the story.

MS. HAGBERG: For the ease of his testimony?

THE COURT: Okay, fine.

BY MS. HAGBERG:

Q. So what did Momenta determine from its study using polypeptide standards?

A. Well, we determined that, first of all, the only thing that we could measure using the poly, I believe it's seven polypeptide standards in this patent would give us an Mp value for molecular weight that made sense with respect to the label claim of the drug. The other aspects of molecular weight, namely, Mw, I recall was outside of that range.

Q. So was knowing that the measurement was Mp important for your progress with being able to report on development to the FDA?

A. Yes, it was. It was very important. Because for the first time we learned how to report a result for this attribute of the material.

Q. And using Mp, that is peak measurement, were you able to

come within the range that is reported in the marketed Copaxone materials?

A. Yes, we were.

Q. How does Momenta typically report molecular weight for its products?

A. Normally, we report the weight average molecular weight or Mw.

Q. And why is that?

MR. HASHMALL: Objection, your Honor.

THE COURT: Yes, this isn't part of the development story.

MS. HAGBERG: All right, your Honor. I'll move on.

I'd like to turn to the issue of, another issue that is relevant. And, your Honor, I just want to call to your attention I'm going to have Dr. Bishop talk about molar ratio now. And before I start, this is the issue that was addressed at the pretrial conference. Your Honor, I believe, said that Mr. Bishop could testify about the product standards that are currently the product characteristics that are currently in the ANDA application, because they've been revised. I was planning to go through how it changed.

THE COURT: Well, I'm sorry, why don't you finish, and then I'll hear from you, Mr. Hashmall. I meant finish what you're saying now. I think there's an objection.

MS. HAGBERG: Or I can just limit him to what is

currently in the ANDA. It's just to put it in context, your Honor, and explain some of the terms. But if that's not necessary, I can go directly to what the current ANDA states.

THE COURT: Mr. Hashmall?

MR. HASHMALL: Your Honor, at the pretrial conference, I could read it into the record, but there was a representation made by Mr. Doyle when we discussed this that all that Mr. Bishop would do would read what's the current specification. I think your Honor said do we really need a witness to do that. And Mr. Doyle said we're just going to have him read and nothing more, and I would say let's limit it to what's --

THE COURT: All right, so let's just do that, put on the record the change.

MS. HAGBERG: Okay. And I think he doesn't have to read it. He knows, he knows the information, so.

BY MS. HAGBERG:

Q. Turning to the issue of molar ratio, Dr. Bishop. Since filing the original ANDA, has Momenta made any changes in the molar ratios that it is listing for what will be its commercial product?

A. Yes, we have made two changes.

Q. And let's focus on the most recent change. Does the most recent change reflect the information that is currently before the FDA?

A. Yes, it does.

Q. And does it also reflect the characteristics of the product that is now under development at Momenta?
A. Yes, it does.
MS. HAGBERG: Could I put Bishop slide three on the screen?
Q. Is this the information that is before the FDA relating to -- is this -- let me -- withdrawn.
Is this the current information reflecting molar ratio for that is reflected in Momenta's ANDA?
A. Yes, it is.
Q. And can you just tell the Court what the current molar ratio is of Momenta's M356, and point out on the chart where that information is?
A. Yes. The information on our current specification is in the last column of table six. Would you like me to read?
Q. Yes, please.
A. It shows a specification range for alanine of 0.392 to 0.462. For lysine, 0.300 to 0.374; glutamic acid, 0.129 to 0.153, and tyrosine, 0.086 to 0.100.
Q. And in terms of the processes that are reflected on this table six of plaintiff's trial exhibit 913-R, which of those, if any, is the current process that Momenta is using?
A. The current process that we're using to manufacture our glatiramer acetate is called process 1.1.0.
Q. And what do the numbers under 1.10 reflect?

A. Those numbers in that column reflect one lot or one batch of material that we have made using this process, and it gives -- these are the observed values for those four amino acids.

THE COURT: And that's 1.1.0?

THE WITNESS: That's correct.

Q. And could you read into the record what those values are?

A. Yes. Alanine shows 0.427; lysine 0.344; glutamic acid 0.136, and tyrosine 0.093.

Q. And have you informed the FDA of these new figures?

A. Yes. We have submitted this information to the FDA.

Q. And if you look at plaintiff's trial exhibit 913R. Just for the record, can you tell us what that exhibit is? And it's -- again, this is a redacted version, but I believe you have the full document in your binder.

A. Yes. This is a communication to the FDA.

Q. And it was the information that was -- could you put that slide back up?

And that information is contained in the communication to the FDA that you just referred to that is the plaintiff's exhibit 913R?

A. Yes, the information on this slide is contained in this communication to FDA.

Q. And are those the amino acid content specification that Momenta intends to use in its final glatiramer acetate product?

A. Yes, they are.
Q. And how confident are you in Momenta's ability to meet the current amino acid content specification?
A. Very confident.
Q. I'd like to turn to another topic, Mr. Bishop. Are you familiar with the steps that Momenta uses to manufacture M356?
A. Yes, I am.
Q. I'd like to focus on step two. What is your understanding of step two or just a general summary of what step two is?
A. Step two is generally known as the depolymerization and deprotection reaction.
Q. And what was the first method that Momenta used when it began to development of M356?
A. I would call it a hit or miss method. We would, basically, run the reaction, this did depolymerization reaction and isolate product at the end, and determine the molecular weight. And if it happened to be in the targeted molecular weight, we were happy.

If it wasn't within the targeted molecular weight, we would make adjustments and produce the next small batch of material. So this it was all in a laboratory scale, using a modified procedure.

Q. Does Momenta still use the hit or miss method?
A. No, we don't.
Q. By the way, what happened if it was a miss?

A. Well, we wouldn't -- this was all on a laboratory scale, so it was not a matter of accepting or rejecting product, in a sort of quality control type of way. But we would basically go back and retry.

Q. And what was the next step that you test, that you used for determining the end point step two?

A. We had, we had read I think it was a line in one of, one of those patents that -- looking at earlier, a line that referred to a test reaction, wherein a batch of material would be used, a test reaction would be run on a batch of material in order to determine the right parameters to carry out that reaction.

Q. And is that a reaction that is determined in the laboratory or in a plant?

A. In a laboratory.

Q. And did Momenta implement -- and what would you refer to that as?

A. A test reaction.

Q. And did Momenta implement a test reaction method?

A. When we were running our early studies in the laboratory, we would run this test reaction, yes.

Q. And when you say "early studies," what time period are you talking about?

A. This is the 2005, 2006 time period.

Q. And how successful were these small -- is it okay to call it a -- how successful were the test reactions for Momenta?

A. The small scale reaction was successful in determining the right parameters for another small scale reaction, and at that time we were only doing small scale reactions.
Q. And so did you try to implement it on a larger scale basis?
A. Yes. Eventually we tried to implement that concept using a small scale reaction to predict what a large scale reaction would be.
Q. And what happened?
A. We were not successful with that.
Q. So what did you do next?
A. So we abandoned the approach of using that small scale test reaction to determine what a large scale reaction should be, and we reverted to another methodology, basically, running a full scale profile run in order to determine the parameters for that reaction.
Q. And what is a large scale profile run?
A. Well, we would take a batch of materials, this is a batch from step one which we call intermediate one, and we would basically divide it into two. So this is a large batch of material divided into two. We would take the first half of that batch and run it in the plant as a profile run in order to determine the correct parameters for the depolymerization. We would then take the knowledge from that profile run and apply it to the other half of the material and execute that, that half of material in that manner.

Q. So you'd be using the testing of one-half of a batch to determine the character, the method for the second half of the batch, is that correct?
A. That's correct.
Q. Did using the large scale profile runs work for Momenta?
A. Yes, it did.
Q. Were there any disadvantages to it?
A. There were many disadvantages to it, yes.
Q. Can you just name a couple; what were the problems?
A. Well, it was very wasteful both of plant time, because plant time is relatively precious and expensive, so it was a waste of plant time, and it was also a waste of material.
Q. Are you still using the large scale batch?
A. No, we are not.
Q. When did you abandon the large scale profile testing?
A. In 2010.
Q. And by the way, what process did Momenta use for its original ANDA?
A. We used the large, the profile run that I mentioned earlier.
Q. So after abandoning the large scale profile test, what test did you turn to next?
A. We implemented viscometry.
Q. And what is viscometry?
A. Viscometry is the measurement of the viscosity of a

solution, in other words, the force that's required to move a solution.

Q. And what is viscosity measuring?

A. Well, it's measuring the force that's required to move or displace a solution. So a more viscous solution like maple syrup up is more viscous and has a higher viscometry reading than something like water.

Q. Did you consider anything else when you were moving, in the process of moving to viscosity to determine any other -- consider any other types of processes?

MR. HASHMALL: Objection. Again, the issue is what the current process is it either infringes or not. Both sides have experts on that issue.

THE COURT: Well, I guess we're getting -- we're moving along here.

I do know about viscosity now, but that's okay. All right, next.

Q. Let me withdraw the question and ask this. Why did you move to viscosity; how would you characterize a viscoscity measurement?

MR. HASHMALL: Objection, your Honor.

THE COURT: That wasn't actually my purpose in saying that. I'd just like to hear about where they went.

MS. HAGBERG: I'm sorry, your Honor, I didn't --

Q. So have you implemented viscosity?

A. Yes, we have.
Q. And is that the current test that Momenta uses?
A. Yes, it is.
Q. I think you helped prepare a slide that describes what a viscometer is and how it works. Can you --
MR. HASHMALL: Objection, your Honor. I mean this would be expert testimony. Obviously, I mean the process is described in the documents and that's I think the process that needs to be evaluated by this Court in determining the infringement issue, and expert on both sides will be discussing it. I don't see how what Mr. Bishop adds to this.
THE COURT: I agree. I think this goes right over the line.
MS. HAGBERG: All right, your Honor, I'll move on.
THE COURT: I understand the progression and now they use, you know, this method.
Q. What is the difference in using a viscometer from the earlier methods that you used?
MR. HASHMALL: Objection, your Honor.
THE COURT: Sustained.
Q. How does the viscometer work?
MS. HAGBERG: Your Honor, it's relevant to our non-infringement argument. He's a fact witness. He has direct knowledge of why and how a viscometer works and how it operates within Momenta.

THE COURT: All right. I don't doubt that. And I guess the question is, this would typically be something that would be in a report and discovered, and there would be a deposition.

When did all this come up?

MS. HAGBERG: Your Honor, there was -- there has been discovery on this point. This is different from the molar ratio issue. This issue came up at the time of the revision. It was --

THE COURT: The time of what? I'm sorry.

MS. HAGBERG: At the time of the revised method that was reported to the --

THE COURT: So who is it that --

MS. HAGBERG: We've had depositions and we've had expert reports on this issue.

MR. HASHMALL: That's right. But Dr. Laird --

THE COURT: Wasn't one of those experts.

MR. HASHMALL: Is one of the experts for Momenta, and Dr. Gokel on behalf of --

THE COURT: And they're going to talk about it.

MR. HASHMALL: Yes.

THE COURT: Okay.

MS. HAGBERG: I'm trying to get him to -- and they had discovery. They took Dr. Bishop's deposition on this issue. So this isn't --

THE COURT: Well, what's he going to say say that I'm not going to hear from your expert where they'll have an opportunity to cross?

MS. HAGBERG: I guess I just wanted Mr. Bishop to tell how and why Momenta is using the viscometer from the perspective of a person in the manufacturing process overseeing the development and what the advantages of the viscometer are, which isn't something that an expert who is not working in developing a product is able to testify about.

MR. HASHMALL: Well, it's still an expert issue. If they're arguing that because of these advantages there's some sort of impact on the infringement analysis, which is isn't clear, it still would be the subject of expert testimony. And if they thought it was important or relevant to the infringement analysis, then their expert should have given an opinion on it.

I mean, the only issue that Mr. Bishop was deposed on is what information have they given the FDA, what have they told the FDA about the process. You know the issue was what are they actually going to be using or is it just tentative or is this real? But as to the details of the process itself, and whether it infringes, that's certainly expert testimony.

THE COURT: I agree.

Q. Turning to what has been implemented. Has Momenta implemented the use of a viscoscity test in manufacturing M356?

A. Yes, we have.
Q. And when did it implement that test?
A. In 2010, 2011.
Q. Will all subsequent, will work on M356 going forward be done with the viscosity measurement for determining the end point of step two?
A. Yes, it will.
Q. Is any additional work going to be done at small scale?
A. No.
MS. HAGBERG: Your Honor, just so the record is complete.
Q. Mr. Bishop, would you please look at PTX-913R, again in your binder.
MS. HAGBERG: And could we have on the screen PTX913R Section 3.3.3.3?
Q. And first can you just say what 913R is?
A. Yes. This is our communication to FDA from earlier this year.
Q. And what is 3.3.3.3 informing the FDA?
A. This informs the FDA of our incorporation of viscosity measurement as our means of in process control or IPC for this step of chemistry.
Q. And what is in process control?
A. In process control is a means of measuring what's going on in the reactor in order to determine when to end the reaction.

Q. And did you also inform the FDA that you were no longer going to be using 1.00 process or the process that was used of 1.0.0?
A. Yes, we informed the FDA that we were moving to this revised process designated 1.1.0.
Q. And has Momenta abandoned the process that it used in 1.00 for determining the depolymerization end point?
A. Yes, we have.
Q. Mr. Bishop, which process will Momenta use in its final glatiramer acetate product?
A. That will be process 1.1.0.
Q. Did Momenta develop any back-up method to measure the end point of step two?
A. Yes, we did.
Q. And what is -- what was the back up?
A. This was I believe referred to as the average temperature methodology.
Q. And what was the average temperature methodology?
A. By measuring the average temperature in the reactor, we would determine the optimal reaction time for that, for that step of chemistry.
Q. Does Momenta plan to use the back up based on average temperature method in its final commercial glatiramer acetate product?
A. No, we don't.

Q. And why not?
A. Because we were successful in our implementation of viscometry when we manufactured four process validation lots.
Q. And is there another back up to the viscometer that you have been talking about up till now?
A. Yes. We have a back up viscometer which now serves as the back up to the main viscometer.
Q. And how does the back up viscometer work?
A. The back up viscometer is a smaller version of the large viscometer which is inserted into the circulation loop of the tank.
Q. And does Momenta intend to use viscometer, I'll call it viscometer number two, in its product going forward?
A. That will be our back up to the main viscometer, yes.
MS. HAGBERG: I have no further questions.
THE COURT: All right.
MR. HASHMALL: Just a few questions, your Honor.
THE COURT: Mr. Hashmall.
CROSS EXAMINATION
BY MR. HASHMALL:
Q. Good afternoon, Mr. Bishop.
A. Hello. Good afternoon.
Q. Couple questions. Do you have in front of you the binder with PTX-914?
A. Yes, I do.

Q. This is Momenta's internal technical report describing the Momenta's in process viscosity control step, control step two that you've been testifying about, right?
A. Yes, it is.
Q. And what's the date on that document?
A. April 14th, 2011.
Q. Are you familiar with this document?
A. Yes, I am.
MR. HASHMALL: Now, your Honor, I offer PTX-914 into evidence.
THE COURT: Okay, admitted.
(Plaintiff's Exhibit 914 received in evidence)
Q. Now you can turn to page MMT0163094.
MS. HAGBERG: Could I just ask that you use the redacted version?
MR. HASHMALL: All right.
MR. HASHMALL: So, Mr. Chase, if you put on the privacy screen, it's 954.
Q. Just to be clear, Mr. Bishop, what we've marked is, this document is the current in place process for the viscosity method you've been testifying about, right; there's no later version of this?
A. I'm not sure if there is a later version of this document or not.
Q. You have that page I asked you about?

A. Yes, I do.
Q. All right. And if you take a look under the graph --
MR. HASHMALL: I guess, Ms. Hagberg, I can't ask the witness to read this aloud?
Give me one minute, your Honor.
Q. So I'm sorry, Mr. Bishop, if you could read the sentence out loud that begins, in the event a failure, in the event viscometer equipment failure?
A. Yes. "In the event of the viscometer equipment failure or the inability to obtain accurate viscosity readings, the reaction end point may be determined using the alternative method described below."
Q. And the alternative method described below is where the time and temperature of the parameters in the determining when the end reaction, is that right?
A. Yes. The average temperature time and point determination.
Q. And this is the current protocol for the process that Momenta's using, correct?
A. Well, we are updating our records to -- we successfully used viscosity during our process validation campaign earlier this year, and so we have this back up in the event that viscometry failed during those process validation runs, since it didn't fail, and we have confidence now in our ability to use viscometry as an in process control, we no longer need this methodology as a back up, and we will be taking that out of our

process henceforth.
Q. But as management now currently stands as far as the Food and Drug Administration is concerned, this is the protocol for Momenta's process, correct?
A. Well, from what we have communicated to the FDA, we have communicated our intent to use viscometry as our in process control for this step.
Q. As things now currently stand, Mr. Bishop, as far as the FDA understands it, the protocol described in PTX-914 is the protocol for Momenta's in process control procedure, currently?
A. Well, this is a research report. This is not on file with the FDA.
Q. But you haven't filed anything with the FDA advising them that you're going to change the back up plan some point in the future, correct?
A. Well, what we have communicated to the FDA is that we planned that we have used and plan on using in process viscometry as a means for this step.
Q. You advised the FDA that in process viscometry is an additional step, not a replacement step, correct?
A. No. We have advised the FDA that we have replaced our profile run from our former process with viscometry for our current process.
Q. Do you have PTX-913A? If you could turn to page 38 in that document?

A. I'm sorry, page number, which page number, please?
Q. I'm sorry 38 of 63.
A. Yes.
Q. Now in this section you see the first paragraph addressed to incorporation viscosity as an IPC?
A. Yes.
Q. And this document has been delivered to the FDA, correct?
A. Yes, it has.
Q. All right. And this is the section where Momenta's referencing a revision to its synthetic process, correct?
A. Yes, it is.
Q. And if you look at the last sentence it says, "For process 1.10 and alternative, in process control method has been added." You see that sentence?
A. No, I don't.
Q. I'm sorry, it's the last sentence in the paragraph.
A. The last part of which paragraph?
THE COURT: Could you repeat that for me, Mr. Hashmall?
MR. HASHMALL: I'm sorry. I was directing the witness to the last sentence in the paragraph.
THE COURT: Okay.
MR. HASHMALL: And, Ms. Hagberg, is that all right we place it on the screen?
MS. HAGBERG: Yes.

Q. This refers to process 1.10. It says "Alternate in process control method for step two utilizing NC2 measurement of solution has been added to monitor and determine the depolymerization end point in step two, correct?
A. Yes.
Q. It doesn't say that it's replacing the prior process that has the reference to the back up plan, correct?
A. I'm sorry, could you repeat that, please?
Q. It doesn't say that it's replacing the prior process that has the back up plan that refers to time and temperature. It says it's been added, correct?
A. Well, in this sentence it describes an alternate. In table 16 on the next page it shows, under process 1.1.0, the word viscosity as our in process control for this step.
MR. HASHMALL: All right. I have no further questions, your Honor.
THE COURT: Pardon me?
MR. HASHMALL: I have no further questions.
THE COURT: All right. Anything further?
MS. HAGBERG: Just one point, your Honor.
REDIRECT EXAMINATION
MS. HAGBERG: Is alternate, by alternate does Momenta mean replacement, it is going to be what they use as shown in the table you referred to?
A. Yes. That clearly is our intent, as I indicated in table

16.

MS. HAGBERG: No further questions.

THE COURT: All right. Thank you, Doctor, you may step down.

THE WITNESS: You're welcome.

THE COURT: Who is the next witness?

MR. DOYLE: Dr. Laird, your Honor.

THE COURT: All right. Why don't we start with Dr. Laird after lunch then, and if you would, if everybody would be back around, you know, take an hour 1:20, 1:25 -- 1:25, all right?

(Luncheon recess)

A F T E R N O O N S E S S I O N

1:30 p.m.

THE COURT: Mr. Doyle.

MR. DOYLE: Thank you, your Honor. May I approach?

THE COURT: Yes.

MR. DOYLE: Sandoz calls Dr. Trevor Laird.

THE COURT: All right, Dr. Laird.

TREVOR LAIRD,

called as a witness by the defendant,

having been duly sworn, testified as follows:

DIRECT EXAMINATION

BY MR. DOYLE:

Q. Dr. Laird, where are you employed?

A. I'm actually self-employed. I have my own business which is involved in training courses and consultancy, mostly for pharmaceutical companies, but also we get involved with all aspects of chemistry, chemicals, flavor, fragrances, you name it, we do it.

Q. And what's the name of your business?

A. Scientific Update.

Q. And at Scientific Update, what types of projects do you do?

A. Mostly we do consultancy in the area of what I call organic process chemistry, but that is a wide subject. So it includes not just organic synthesis, process development scale up, but anything that to do with the finished product as well, which might be related to crystallization, solid state forms, et cetera, that are needed on the interface between the chemistry and the formulation.

Q. And do these projects sometimes involve synthesis, design and optimization?

A. Yes. Synthesis design I really call process research. And the optimization, that goes with that and to all scape is really more process development. But it's a continuous -- there is no real defined interface. But the terms are used separately.

Q. Can you describe a little bit more in detail what is organic process chemistry and scale up?

A. Well, the organic process chemistry is usually on the

design of the synthesis to a target drug. So always in developments we have a target, it's what the discovery chemists have decided is maybe a development compound or if you've work for generic you know what the end drug is. So the target is really to design the synthesis in the best way using appropriate raw materials, low cost raw materials if possible; whereas the scale up is really more the development of each individual step of that synthesis, and then taking that from the laboratory, laboratory, and then into the pilot plans, and then finally to full scale manufacture.

Q. And you mention that you do consulting services, provide consulting services to different types of pharmaceutical companies. Would those include what are referred to as branded companies and generic companies?

A. Yes, they would include branded companies Pfizer, Merck, et cetera, but also small biotechs, what I call emerging pharmaceutical companies, and also generics as well.

Q. Have you consulted for any of the companies involved in this case?

A. Yes, I have. I've consulted for Teva, I can't you details, but it was involving an urgent request of John, an urgent problem to solve a problem, manufacturing problem. And I've consulted for Novartis, subsidiary called Ciba Vision, which is actually involved in the manufacture of contact lenses. And the problem there was again manufacturing problem related to

polymerization and producing polymer that goes into the contact lens.

Q. Before 1994, were you teaching at companies on issues of organic process chemistry?

A. Yes, I was. When I started the company in 1989, I wrote a training course called chemical development and scale up, and this is being taught to companies worldwide, I think about 25 different countries, thousands of people have attended the course, and in before 1994 I was teaching this to Pfizer to Glaxco, to smaller companies as well.

Q. And did your courses include teaching regarding test reactions?

A. Yes. I mean in the course definition of test reactions, we teach people how to optimize processes either by looking at the effects of changing parameter on the yield qualities, impurities, et cetera of the product. I also have this scale up. So this development work is mostly test reactions. We're looking at the particular chemical reaction and testing it out to see what, if you change the temperature, concentration, reagents, et cetera, what effect that has on the product and the process.

Q. And is there another term which would be a subset of test reactions as has been defined by the Court that was part of your course material back in 1994?

A. Yes. I mean, in my reports on this case, I used the word

test reaction originally as a synonym for use test. And use test is more of the term that I would normally use in industry. And by use test, I mean testing a batch of a material usually in a laboratory before you commit to the whole of that batch in production, or maybe it could be a raw material as well.

Q. Were both test reactions as amended by the Court and use tests common in 1994?

A. Yes, they were.

Q. Now, what did you do before starting your company scientific update?

A. Well, when I left the University, I joined the company called Imerial Chemical Industries, its ICI. It was an enormous company in 1973, when I joined 150,000 employees. It is about the size of DuPont. It doesn't exist any more because of fragmentation and all sorts of business deals, let's say. So I spent seven years there, different divisions, not to do with pharmaceuticals, though it, was all to do with agrochemicals, color chemicals, electronics chemicals, et cetera.

Q. Then did you move to a pharmaceutical company?

A. Yes. I joined Smith Kline and French as it was then known in 1979. It's now, it's part of Glaxo Smith Kline. And eventually I became the head of development, their chemical development where I had about 30 BSE scientists working for me. And I was also in charge of the pilot facilities at the UK

site. That was a very strategic position, because all of Smith Kline's drugs which were in development came through that site, because at that time they didn't have a pilot plan in the U.S.A. So I was effectively responsible for the small scale manufacture of all Smith Kline's drugs prior to launch, prior to transfer to manufacturing sites.

Q. Was it from Smith Kline that you then moved to form your own company, Scientific Update?

A. Yes, it was. I tried to improve my staff by getting continuing education, because I felt that sometimes people with a Ph.D. rely on information they got before that Ph.D. and don't update it. But I had not much success in getting people come and do training. So I felt, well, there is a gap in the market here, why don't I do it myself. And that's proved to be an excellent decision.

Q. Are you on any scientific advisory boards?

A. Yes. I have been on a lot of scientific advisory boards for smaller companies. But, again, they've got subsumed into multi nationals and I've lost those positions.

But at the moment I've just recently taken on science advisory board with a company Sand Chemicals in Switzerland which is a peptide and polypeptide manufacturer.

Q. Could you briefly describe your educational background before you went into industry?

A. Yes. I studied chemistry at Imperial College, London

specializing in organic chemistry for the last year, and then I did a Ph.D. at another college in London, John Cass College where I got my Ph.D., and there were four publications that came out of that. Then I moved to Sheffield University in the north of England and had a very productive period where working for Professor Olis, and that was -- resulted in I think about 11 publications in the three years.

Q. And in addition to those publications in your academic career, have you written any other articles or book chapters?

A. Yes. I've written several book chapters once I've been in industry. Some of these have been just on general chemistry, some have been to do with particular applied subjects, such as amazingly solar energy, and those are being more focused on the topics of discussions today, which is chemical development and scale up.

At the time I wrote a chapter in comprehensive medicinal chemistry in -- well, it started about 1988 and it was published in 1990. There weren't really many publications that said anything at all about the subject of process research development and the interface between the laboratory and manufacture. And so this review was one of the first sort of set down the principles. I suppose that then tempted me to leave Smith Kline, because I felt, well, I've got the principles, I can put that into a course and hopefully make some money as well.

Q. Do you serve on any editorial boards?
A. Yes. I'm actually chairman of the editorial board for the Journal Organic Process Research and Development, which is an American Chemical Society publication. I was actually the instigator of this particular journal in the mid 1990s. I persuaded the American Chemical Society and the Royal Society of Chemistry in England to put up some money so that we could start a new journal, focus much more on industrial aspects of organic chemistry, but with some chemical engineering interface as well. I was appointed the editor in 1995. The first issue came out in 1997, and I'm still editor, and renewed until 2014.
Q. How has the journal done?
A. It's highly regarded. There wasn't much there before, so it didn't have any of competition, but it is well regarded in the industry worldwide. It has papers from all over the world, from Japan, India, et cetera, as well as Western European, the States.
Q. Do you write editorials for the journal?
A. Yes, I do. I try and be a little bit controversial or maybe a bit humorous. And so I try and do an editorial on each of the six issues every year. So in the past 15 years I've probably written 70 or 75 editorials, covering a wide range of subjects. I mean, the subjects are I've chosen are sort of dear to my heart, the academic industry interface, generics industry, crystallization issues, all sorts of things. But one

of the things, a couple of editorials have to do with reproduce-ability.

Q. And why have you chosen that subject to speak on?

A. Well, it was always an interesting subject to me when I was at Smith Kline. Because some of our colleagues in the U.S. would give as a procedure that we had to scale up in the UK. And sometimes we couldn't even reproduce it in the laboratory, never mind scale it up. So it was clearly some deficiency in the way laborites were done.

And a lot of chemists find difficulty repeating procedures in the literature, and in patents as well. So that's been a particular interest of mine. It's been reinforced by requests from lawyers for my company Scientific Update to take a procedure and patent, and then try and get a company to repeat that. But what we have to do is to take, let's say, the ten lines of the patent experimental procedure and then write it out in a manner of the person of skill in the art. So it's almost like a set of instructions, almost like a batch record for the company to actually repeat this procedure. And what we have to do is to make the assumption that a person of skill in the art would do, that if it says you heat it to 50 degrees, does he mean between 45 and 55, or how fast does he heat it, and these sort of things which are not usually written down, but a person of skill in the art probably can make a good assumption as to what should be done.

Q. From your last answer, it sounds like you've been involved in some legal proceedings as an expert in the past?
A. Yes. I mean, those things I've talked about now are sort of prelegal proceedings, I think deciding whether to litigate or not. But, yes, I've -- in my CV I've listed a number of cases where I've been involved, testified at trial in the U.S. I think three times.
Q. Do you consider yourself to be an expert in the field of organic process chemistry?
A. Yes, I do.
Q. And does that include expertise from both an academic and an industry perspective?
A. Yes, it does.
Q. And does that include being an expert in manufacturing the pharmaceuticals?
A. Yes, partly because the interface I have is between organic chemistry and mechanical engineering. And a lot of chemical engineering involves issues to do with, to do with scale up, and scale up is really the essence of getting the problem sorted out before you go into manufacture.
Q. I'm going to have put on the screen now paragraph ten from your expert report, which includes a definition of the person of ordinary skill in the art from your perspective. Do you see that?
A. Yes. Thank you for expanding it.

Q. And does this state your view as to the qualifications of a person of ordinary skill in the art with regard to the issues of organic chemistry and organic process chemistry that are relevant to this case?
A. Yes, it does. I mean, I've mentioned a Ph.D. in organic chemistry or equivalent, partly because I find that some BSCs in organic chemistry can be very expertly in development in scale up. So not necessary it's the Ph.D. or the equivalent. I think that's perhaps slightly different from some other definitions.
Q. And in 1994, were you a person of at least ordinary skill in the art?
A. Yes, I was.
Q. And would that also apply to 1995?
A. Yes. I still am.
Q. And were you here for the testimony of Dr. Gokel and Dr. Sampson?
A. Yes, I was.
MR. DOYLE: Your Honor, Sandoz and Momenta offer Dr. Laird as an expert witness in organic and process chemistry.
THE COURT: Any objection?
MR. WIESEN: No objection, your Honor.
THE COURT: All right. The Court accepts Dr. Laird as an expert. Go ahead.
MR. DOYLE: Thank you, your Honor.

Q. I'd like to start this afternoon, Dr. Laird, with the topics of predetermined time and test reactions. And, Dr. Laird, do you understand that the Court construed the claim term predetermined to mean determined beforehand?

A. Yes, I did.

Q. And do you understand the Court has construed the term predetermined by test reaction as determined beforehand by a reaction carried out to determine results of varying reaction conditions?

A. Yes, I understand that.

Q. And are you applying the Court's claim constructions in your testimony today?

A. Yes, I am.

Q. Were test reactions as construed by the Court commonly known in 1995?

A. Yes. The test reactions defined by the Court are an essential part of development chemistry. So when you are trying to optimize a process, you're looking at the way in which the process variables have affect on the end product that could be a quality or yield or sometimes the physical properties of the solvent, everything to do with that material. So these are all really done by test reactions designed to experiment with the variables.

Q. I'd like to just take a brief look at your course that extends back into the 1990s.

MR. DOYLE: Could we see PTX-0775, please?

Q. What is PTX-0775?

A. This is the first page of many to do with a particular model that comes from the course that I wrote in 1989, to do with development, chemical development and scale up of chemical processes. And this is probably a series of about, power point slides. The original version that I wrote wasn't in this format, but the wording is the same.

MR. DOYLE: Could we see page 16, please?

Q. And does this make reference to what you were describing earlier as use tests?

A. Yes. I mean obviously use test is a subdivision of test reactions as explained by the Court. And actually use test is mentioned twice on there, that the one at the top and the fifth bullet point which talks about analyzing all raw materials and intermediates, except reactives and carry out use tests prior to scale up.

So the idea of use test is that if you have a batch of materials where there may be things that you can't analyze for -- and this is often quite true with intermediates -- you want to test it out in the laboratory before you commit kilograms and tons of material to technique for might be a lot of waste. So you try that in the lab. If it works, then you scale it up and do the full batch. If it doesn't, you find out what the problem is.

Q. Are you familiar with end process controls in the manufacturing pharmaceuticals?
A. Yes.
Q. And have you discussed those in any of your articles or have you included discussions of in process controls in your courses that you teach?
A. Yes. It's discussed in articles and also in the courses. We feel it's a very important aspect of process development that people should be following reaction. I mean, this occurs in academia as well, that you follow reactions with an in process monitoring. And in the plants if you can put the control aspect in the reactor, then it means you'd know when a particular reaction is finished.
Q. And can you elaborate a little bit more on just what is an in process control as opposed to a control in the manufacturing that's not in process?
A. Yes. I mean, in process control is monitoring the progress of the reaction, so that at a certain time when you want to go onto the next part of process, you can, you can decide what to do. Some in process controls have a feedback so that it actually goes into the system. So sometimes that happens with even with temperature, for example, our feedback loops which I put a monitoring into a control position.
Q. And are you also familiar with using test reactions to predetermine the time and temperature of reaction conditions?

A. Yes. I mean, I would say that most of the projects that I worked on have used test reactions, because this is a standard part of chemical development.

Q. And in your teaching and consulting with companies, do you have a preference as between in process controls and test reactions?

A. Generally prefer in process controls, if you can do it. But test reaction, particularly use tests, certainly have their value in the sense that you don't always know what you're measuring on a batch. So sometimes it is necessary to do those tests.

Q. And what is the basis for your preference of in process controls if you can develop one?

A. Well, it's usually instantaneous. It tells you what you wanted me -- whereas, use testing you have to either do it beforehand, but there's always a problem if you do a use test that you're doing it in the laboratory; whereas, the actual materials being carried out in the plant. And so sometimes the things vary. And usually the thing that varies most is the time that it takes much longer to heat things up in the plant, cool them down. So something that takes, you know, 24 hours in the lab will take maybe, maybe as much as 48 hours in the plant. So you have to allow for these differences in times.

Q. Let's turn to the patents. Could we have the 898 patent claim one, please? And looking specifically at the inset in

the first paragraph, there is a claim limitation wherein said reaction takes place for time and at a temperature predetermined by test reaction. Do you see that?
A. Yes, I do.
Q. And is it your understanding that this claim limitation is not only in claim one, but also in dependent claim two of the 898, and in claims one and two of the '430 patent, claim one of the '476 patent, and claim one of the '161 patent, all contained the same limitation; is that your understanding?
A. That's right, they all contain the same limitation.
Q. And is your testimony here this afternoon with regard to this claim limitation, applied to that claim limitation in all of those claims?
A. Yes, it does.
Q. And did you prepare just a small demonstrative to demonstrate where this is found in the patents?
A. Yes, I did.
Q. And is this the demonstrative that you prepared?
A. Yes. It, more or less, says what you just said.
Q. Okay, thank you. Now, are you familiar with Sandoz's proposed manufacturing process as described in its recent communication with the FDA?
A. Yes, I am.
Q. Please turn to PTX913R, which you will have the non-redacted version, but on the public screen we will have a

redacted version.
A. PTX-913 was it?
Q. Yes, PTX-913.
THE COURT: And, Doctor, everything will also be on the screen.
THE WITNESS: Thank you.
Q. Have you seen this document before as it appears in your binder as opposed to on the public screen?
A. Yes, I have.
Q. Please turn to page 24 in PTX-913.
A. Okay, I have it.
Q. And what does this depict regarding the Sandoz manufacturing process?
A. It depicts a four step process for making glatiramer acetate, starting with N-carboxyanhydrides of four --
Q. Dr. Laird, perhaps if you want to use your -- do you have your laser pointer?
A. Yes.
Q. If you care to, it might help?
A. Yeah, I don't know if will help with the writing. So the it's a four step process for manufacturing glatiramer acetate, and it starts with the N-carboxyandhydrides of the four amino acids were are labeled, here which is the R group. And the first step is the polymerization to give the isolated intermediate one, which is the protected in two places. The

second step is the conversion of that into the intermediate two, using HBr acetic acid, including phenol and some extra water as well. Again, that's an isolated intermediate. This intermediate two is converted then with piperdine and water, to give the intermediate three, and then finally that intermediate three is purified by defiltration and to give the final glatiramer acetate.

Q. In your opinion, Dr. Laird, does Sandoz's process meet the claim limitation wherein said reaction takes place for a time and at a temperature predetermined by test reaction?

A. No, it does not.

Q. And why is that, if you could just summarily tell us at this point, and we'll go into it in some detail?

A. Yeah. Well, basically, this is focusing on the step I think we were discussing, that is the step here which is to do with the HBr acetic acid process. This is not -- the end point of this process is not via a test reaction using viscometry.

(Continued on next page)

Q. And could you briefly explain what a viscometer measures?
A. Viscometer measures viscosity, which is as we've heard before a sort of resistance to flow is the way I like to describe. It's anything that's viscous doesn't flow very well. As soon as you heat it, it becomes more mobile and it flows. A bit like honey, really.
Q. And again, can you indicate where it is in the process that the viscometer is used in the Sandoz method?
A. Yes, it's used in conversion of intermediate 1 into intermediate 2.
Q. And what is your understanding of how many viscometers Sandoz uses in its process?
A. Yes, I've seen the batch records the Momenta subcontractor uses and there are two viscometers used in the process. One is a long reach viscometer, which goes into the large reaction vessel, and the other one's on a recirculation loop as a backup.
Q. Do both of these viscometers work in the same way?
A. Yes, they work by the way I've described, by making waves. They don't move at all. It's a static piece of equipment, it's measuring a resistance to a wave and that is the function of the energy, to make the wave that ends up being in proportion to viscosity.
Q. Have you prepared a demonstrative with regard to the Sandoz process involving viscometers?

A. Yes, I have.
Q. Could we have slide 4, please? And is this the demonstrative that you participated in preparation of?
A. Yes, it is.
MR. WIESEN: Your Honor, I just need one moment, because I don't think we've gotten this slide as part of Dr. Laird's data. Let me check and see. Do we have this?
MR. DOYLE: Perhaps not. I think it may have --
THE COURT: We've seen it with Dr. Bishop.
MR. DOYLE: I think we sent it to you with Dr. Bishop.
MR. WIESEN: No problem.
THE COURT: Do you have a copy, though?
MR. WIESEN: We do now.
Q. Would you describe what is shown on slide 4?
A. Yes. It's a bit of a schematic. It's not really like this in practice in the sense that all I'm showing is the reaction of the vessel here, but this is where the reaction takes place. In practice there's an agitator, all sorts of other things going into it, so what's shown is just the viscometer. It's a long tube and the business end of it is actually the tick here, which is where the measurement takes place. So it measures the viscosity and also measures the temperature very accurately at the same point at which the viscosity is measured.
And then the batch is recirculated around a loop and the smaller viscometer goes into the recirculation loop so it's

actually measuring the viscosity at different places. But they both operate by the same system. As far as I understand, they're made by the same British manufacturer.

Q. And does the viscometer shown on slide 4, do those viscometers conduct a test reaction to measure viscosity?

A. They do not. There's no reaction here, they're just measuring a physical property of the fluid in the tank, and that property, the viscosity is related to the progress of the action.

Q. And in the Sandoz process for making copolymer-1, what's the end point of the step 2 process?

A. The end point is the viscosity at a particular temperature and this viscosity in temperature has been previously correlated with the molecular weight of the glatiramer acetate. So the end point is the viscosity and temperature which would give a molecular weight of about 7300.

Q. And how in fact does the reaction, the step 2 reaction, how is it stopped?

A. Well, it's very important to stop the reaction once you want to what we call work up and isolate the product. So it is stopped by adding the reaction mixture into water, in the lab probably what chemists do is add water because that's the convenient thing to do, but in the plant it's simply safest to add it to water and that stops the reaction very quickly.

Q. Is there a term of art in the industry for doing that?

A. Quenching is usually what some people call it. Drownout is another one.

Q. Now, you stated earlier your opinion that the Sandoz process that you just described does not meet the claim limitation wherein said reaction takes place for a time and at a temperature predetermined by test reaction. Now that we've seen more about the viscometer process, can you describe in a little bit more detail your opinion as to why that process, the use of the viscometer, does not meet that limitation?

A. Yes. When this process is carried out, the instruction to the process operator in batch records says maintain the reaction at 22 plus or minus 2 degrees with the aim of obtaining a temperature of 21 degrees. That's a strange way of doing it, I know. But the aim is to get 21 degrees, and then they measure the viscosity, so is process operator is monitoring this viscosity -- sorry, is monitoring the temperature and the viscosity, and he has a table of correlations, different temperatures at points of about .2 a degree apart. So when he's measuring the batch temperature, say, that's 20.3 or something like that, he looks on the chart he knows exactly what the viscosity is that he has to stop the reaction at to then go on eventually to in the next step to give the glatiramer acetate of the desired 7300 molecular weight.

So he's just looking at viscosity, he's not looking at

the time at all. In fact, the time will vary quite a bit depending on whether the temperature is at the top of the range or at the bottom, so we saw in some of the, in some of the batch records that the temperature in some batches was 20.9, and on other batches it was 20.3. The difference between those in terms of the time for the reaction was from 38 hours to 50 hours, so it makes a big difference in the time. So from this point of view time is not really a very good measure of the end point of the reaction, whereas the viscosity is measuring a direct property of the correlates in the solution with the desired properties that you'd want to have. So it's a very much better correlation and doesn't use time at all.

Q. Are there any other parameters involved in this reaction in addition to the temperature as you just described that can affect the duration of step 2?

A. Yes. I mean, first of all, the quality of the materials going in, so the intermediate 1, if there's any batch-to-batch variability in the polymerization, then that's where -- maybe effect the time taken in the process. The concentration should be fixed, but you never know what a process operator is going to do. Sometimes you get a bunch of viscosities that will more or less give you a result in spite of the process operator, whereas if you rely on time, if he's done something wrong, you'll never detect it.

Q. Now, in developing the chart that you described that

correlates the different temperature levels with the viscosity levels, in the laboratory did Momenta utilize test reactions to develop that chart for the correlation between the temperature and the viscosity?

A. In the Court's definition of test reaction yes, yes, they have, because as I said, it's more standard process of chemistry and, yes, they are correlating the properties with the viscosity, so yes.

Q. And what's your understanding of how they did that in the laboratory at Momenta?

A. They carried out the process in the lab monitoring the viscosity, but also taking samples out and converting them through to final glatiramer acetate and then measuring the molecular weight. And so as a result of all these samples that they took out at various times, they would then build up a correlation between the viscosity and the molecular weight of the glatiramer acetate.

Q. Now, what advantages, if any, does Sandoz achieve in your opinion with its viscometer model as opposed to a time and temperature model?

A. I think it's the accuracy of knowing when that end point is. Because you're actually measuring the property of the solution. Viscosity is proportional to the species they have in the solution, the concentration, and of course very temperature dependent as well, so it is giving a very accurate

picture of the end point. If you do the time, there's all sorts of problems with having an end point with time.

In our courses we recommend that people do not use time as an end point but try and have some sort of analytical measurement that correlates with the process, because we've seen people -- "come a cropper" I believe is the English term -- using time as a measure of completion when the reaction may not be finished.

Q. Mr. Gueverra, can we have slide 5? Is slide 5 a graph that you prepared, sir?

A. Yes, it is.

Q. Is it a summary of your thoughts with regard to greater accuracy from using the end process control of viscometer?

A. Yes, it is. One of the advantages of viscosity is that you don't have to take samples out and analyze them or convert them through. You're continuously recording the data. I think Momenta's subcontractor detects records every five minutes, so you get an instant and realtime data rather than relying on, say, the test reactions that you may have done previously which may not even be on the same batch of material. Then you're not going to get the accuracy that you need from that.

So the measurements on the reaction of the whole batch, that means if the process operator has done something silly or cleaned the reactor out and left a bit of water there, you're still going to get an end point for the reaction. So if

something goes wrong, you know exactly where you are. But with time, you know, you don't really know what's happening in the batch. It's the fact that it's measuring an intrinsic property of the protected copolymer that is important that directly correlates with the result that you want to get.

Q. Dr. Laird, just a couple of wrapup questions with regard to the viscometer model and this particular limitation in the claims. Do you have an opinion on whether the chart correlating temperature and viscosity that is part of viscometry method, was that developed by correlating time with viscosity?

A. No. It was developed by correlating viscosity at a certain temperature with the -- and then by taking samples out to convert them through to the glatiramer acetate, so it was really temperature, viscosity and molecular weight of the prime product.

Q. Dr. Gokel testified there is a general correlation between time and termination of step 2 based upon viscosity. Do you have a response to that?

A. I think he is just using in general terms that all reactions have a time dependence and we always measure the time of every operation, every batch record that I've ever seen, it's almost compulsive, you have to know the time these particular operations are carried out, but it's not a very useful -- certainly from a scale point of view, because time

varies so much from manufacture to manufacture.
Q. In your opinion, is time the end point of the Sandoz step 2 reaction?
A. No, it is not.
Q. And what is?
A. It's the viscosity measurement in the correlation at a certain particular temperature.
Q. Dr. Laird, I'd like to move at this point to different claim limitations involving using HBr to cleave polypeptides. Are you familiar with those limitations that have already been shown to the Court multiple times in this case?
A. Yes, I am.
Q. Were you here for Dr. Zeigler's testimony on the HBr acetic acid?
A. Yes, I was.
Q. I want to obtain your independent opinion, hopefully relatively briefly, on some of the issues that he addressed, and the first issue is would a person of skill in the art in 1994 have known that the HBr acetic acid reaction could be used to cleave peptide bonds in copolymer-1?
A. Yes, there were a number of articles that expressed that view and some had experimental verification.
MR. WIESEN: Your Honor, we just have a general objection to duplicative testimony from two experts of the defendant. I realize there are different defendants here, but

it sounds like we're going to go into exactly the same arguments we heard from Dr. Zeigler.

MR. DOYLE: We're going to do it very briefly to clear up what we believe was a misimpression that we think was created yesterday with regard to how these two references relate to each other, but other than that we're going to move on.

THE COURT: All right, I'll let you do that.

MR. DOYLE: Thank you.

Q. Just briefly, DTX 3329. Are you familiar with DTX 3329, which is an article Idelson and Blout from 1958?

A. Yes, I am.

Q. And to you as a person of skill in the art does the Idelson and Blout 1958 document disclose removing protective groups with HBr acetic acid?

A. Yes, it does.

Q. As a person of skill in the art based on this article was peptide cleavage observed and reported in this article?

A. Yes, it was. Idelson mentions that some of the substrates show extensive peptide bond -- one of the substrates, I should say, shows extensive peptide bond cleavage.

Q. And is this the portion of the Idelson Blout 1958 article that you're referring to?

A. Yes. He says that hydrogen bromine in glacial acetic acid has not been found to be a useful reagent. What he's referring

to is the debenzylation. The reason it's not useful to him is he wanted the debenzylation and he didn't want the peptide cleavage, so he's saying, well, the problem is the peptide bond cleavage and he shows in a table later, which is actually under there, the extent of the cleavage. So the first example, LPG's going from depolymerization of 140 then to 50, and in fact, we had an example that show peptide bond cleavage, but they're not done in acetic acid.

Q. Let's try to deal with the other references in a summary way. I first would refer you to DTX 1781, and are you familiar with this reference?

A. Yes, I am. This is -- I'm looking at the degradation of polymer amino acids, mostly biodegradations, but he doesn't mention peptide bond cleavage in that degradation.

Q. And DTX 1782, are you familiar with this reference?

A. Yes, I am.

Q. Is this often referred to in this case as the Applequist 1962 reference?

A. It is.

Q. And does it indicate peptide cleavage result of the HBr acetic acid treatment?

A. Yes. He refers to the Ben-Ishai paper which we've heard before from Dr. Zeigler, and using that method, then he says he observed a small amount of peptide cleavage. I think he's -- on peptide bond 1000 I think is mentioned in this particular

paper.
Q. DTX 3328, are you familiar with this reference? This is an article by Dr. Blout from 1956.
A. Yes, I'm familiar with the papers. I'm not familiar with the numbers.
Q. And in particular, is this another article showing peptide cleavage as a result of HBr acetic acid treatment?
A. If you could put the paper up.
Q. Yes.
A. I'm sorry, what was it again, the number?
Q. This is DTX 3328. If we could go to the first indication of where the hydrogen bromide treatment is referenced.
A. Yes. It's just in the question you said hydrogen bromide acetic acid and in this, it identifies just hydrogen bromide has been shown to affect cleavage, so actually in acetic acid. It's just hydrogen bromide straight on.
Q. Finally, these references showing peptide cleavage as a result of HBr acetic acid treatment, do you -- are you aware of any indications that this was accepted in the art by knowledgeable people as something that would occur?
A. Yes. There's a mention in the excellent review by Katchalski and Sela on page 410, if I remember correctly, and there, I don't know if you're going to put that one out, but from my memory, the key quotes, the last reference of Blout and Idelson with hydrogen bromide, and mentions here that poly

benzyl glutamate was reduced in molecular weight from 680,000 down to 135,000, so it's a degradation there.

Q. And is there a specific statement regarding degradation in the Katchalski Sela article?

A. Yes, he says it reports slight degradation. Well, it's a factor of about five, so it's a very important slight, but significant, I would say degradation of a poly amino acid and to me Sela is one of the authors of the patent, so it indicates to me he certainly was aware of HBr causing degradation.

Q. And was this article by Katchalski and Sela, was this an influential article at the time?

A. Yes, it's about 250 pages. It's subtitle could be all you need to know about poly amino acids.

Q. And finally --

MR. WIESEN: Your Honor, that one I'm going to object to, in that I don't believe we have testimony that Dr. Laird was around in 1958 when that article was published.

MS. BLOODWORTH: I'll further go into this.

Q. Dr. Laird --

THE COURT: Okay.

Q. When you were around, was this article seminal enough that it was still highly regarded and important in the field?

A. Yes. I'll agree, I wasn't a child prodigy, yes. Yes, it was an important article. The usual measure of that is the number of people that refer to it on citation, etc.

Q. My final question, I think it's my final question here, close to my final question in this area. Do you need to combine the Idelson and Blout with the Appelquist with the Hayashi and Blout and Katchalski and Sela, do you need to combine these to reach your conclusion as to peptide cleaving as a result of HBr acetic treatment would have been known to a person of skill in the art in 1995?

A. You don't have to combine because one reference particularly, Idelson and Blout would give it to you straight away. All the others mention work done, and Hayashi mentions it, so on their own you could see one, of course more is better, but certainly that is mentioned in the literature in more than one occasion.

Q. And in your opinion if a person of skill in the art wanted to make copolymer-1 of a smaller molecular weight, would that person have been motivated in 1994-1995 to choose HBr acetic acid to do that?

A. Yes. Because clearly if you're doing debenzylation the literature shows debenzylation HBr acetic acid and if you want to cleave the peptide, then it's obviously advantageous to use the same mixture which you know doesn't cause any further problem, so from a manufacturing point of view, it's like putting two steps together.

Q. And in your opinion in 1994, 1995, would a person of ordinary skill in the art have expected HBr acetic acid

treatment at room temperature to result in partial cleavage of peptide bonds in copolymer-1?

A. Yes, they would.

Q. And that partial cleavage would mean what in terms of the molecular weight of the copolymer?

A. Peptide bond cleavage is going to lead to reduction in molecular weight, so you would expect that from reading the literature that by treating with HBr acetic acid you could by choosing the appropriate duration of the reaction to some extent choose the end point of it in terms of reduction in molecular weight.

Q. I'd like to move on to a few of the other process limitations which are included in the asserted claims. Could we have Dr. Laird's slide 3, please? Do you have opinions, sir, with regard to the claim limitation, reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1?

A. Yes, this limitation I think it's already known that this would occur from what I've said earlier.

Q. And there's been quite a bit of testimony on this, but which references would one look to to find this particular process limitation?

A. I'd be looking at Idelson and Blout and the ones we've mentioned.

Q. And with regard to copolymer-1 specifically, are there any

indications in the synthesis of copolymer-1 that one should use hydrobromic acid to form the trifluoroacetyl copolymer-1?
A. Yes, we would be looking at the '550 patent and the Teitelbaum paper in whatever it was, Journal of Immunology.
Q. And in looking at the second limitation, selecting a predetermined molecular weight profile. Would that process step be known to a person of ordinary skill in 1994, 1995 based on the art relating to copolymer-1 that existed at that time?
A. Yes. The '550 patent and Teitelbaum both mention molecular weights, and the process to carry out the chemistry that leads to those molecular weights.
Q. And does the Teitelbaum article also teach achieving a desired molecular weight?
A. Yes, it does. The Teitelbaum article, as we've seen many times on the screen, has two batches of copolymer mole and the molecular weights are both around 23,000.
Q. And was that the goal of the inventors, the authors of that article, to achieve a molecular weight at around 23,000?
A. Yes, I think it was, yes.
Q. Now, turning to a couple of additional claim limitations relating to process, the time and temperature process limitations. Could we have Laird slide 4, please? And is it your understanding that this limitation, wherein said protected copolymer-1 reacted with hydrobromic acid for about 10 to 50 hours at a temperature of about 20 to 28 degrees centigrade, is

found in claims 2 of both the '898 and the '430 patents?
A. Yes, it is.
Q. And, sir, have you reached a conclusion as to whether the time and temperature steps of these claims would have been obvious in the 1994-1995 time period?
A. Yes, it would have been obvious from some of the papers that we have mentioned, and perhaps a couple of more that we're going to mention.
Q. Yes. Let me just mention one reference that we haven't seen yet and then we'll do a summary slide with regard to the others. Have you relied in reaching your opinion on the Yaron 1958 reference, which is DTX 3233, in reaching your conclusions?
A. Yes, I have.
Q. And what is it about that article that you relied upon?
A. It's in relation to the end of that article, that it's using a time and a temperature HBr less than 2 degrees for three days during the debenzylation and so that is amongst the papers that describe the time and temperature. Now, if you take the normal chemistry rule that a rate changes by a factor of two for every ten degrees, then that will take you into the same sort of region as the limitation, so two degrees for three days, 72 hours would equate to 18 hours at 22 degrees. So it would have been clear to a chemist skilled in the art that that was within the region.

Q. Could we have very briefly DTX 3233 on the screen? Is this the article you've just been discussing?
A. It is, yes.
Q. What page were you referring to where the time and temperature is indicated?
A. 97 in the second paragraph.
Q. And now if we could have slide 1. Have you prepared a summary slide of these various articles dealing with the HBr acetic acid reaction with regard to time and temperature?
A. Yes, I have. Hopefully it's going to come up.
Q. Is this the chart you prepared?
A. Yes, it is.
Q. And are the Idelson, the Ben-Ishai, Ben-Ishai and Yaron articles all ones that you've discussed today?
A. Yes, they are.
Q. And what do they indicate with regard to time and temperature for this reaction?
A. That a person skilled in the art would carry out HBr acetic acid reactions by extrapolation from these references. Ben-Ishai overnight at room temperature comes directly within the claim limitation, but by using the chemist that's skilled in the art and the rate factor, the bottom three come within that region of the limitation.

Unfortunately, Idelson is an example of what I call about reproducibility, there's not really a temperature, so you

can't see the exact correlation, but clearly if you reduce the temperature, the time is going to take longer, so it's obvious to a person of skill in the art.

Q. One final question. To reach your conclusion as a person of skill in the art that the time and temperature limitations of the claims we've been addressing were obvious, do you need to combine these references?

A. No. A chemist could look at some of those and extrapolate. Clearly, it helps to have a few more to back that up.

MR. DOYLE: Nothing further. Thank you, your Honor.

THE COURT: All right. Mr. Wiesen.

MR. WIESEN: Your Honor, we have some binders to hand out.

(Pause)

CROSS-EXAMINATION

BY MR. WIESEN:

Q. Good afternoon, Dr. Laird.

A. Good afternoon.

Q. Could we put up Dr. Laird's slide number 3, please?

Dr. Laird, I just want to make sure I understand the scope of the opinions that you're giving here today. You focused only on the particular limitations that are on this slide number 3, correct?

A. That's correct, yes.

Q. So for claim 1 of the '808 patent, the '589 patent, the

'898 patent, the '430 patent, the '476 and the '161 patent, you're focused only on the reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1 limitation, correct?

A. In that discussion I was, yes.

Q. You're not giving an opinion that claim 1 itself is obvious, right?

A. I need to read the whole of the claim at first, but I --

Q. During your direct you didn't offer an opinion that all of claim 1 was obvious, correct?

A. Could I just look at claim 1, just check it out before I give an answer?

Q. If you can answer my question --

THE COURT: You haven't given that opinion in your direct, right?

THE WITNESS: No.

THE COURT: Okay, fair enough.

Q. And similarly for claim 1 of the '898 patent the only opinion you gave on your direct is that in the prior art you could find references to selecting a predetermined molecular weight profile, correct?

A. That's correct, yes.

Q. You haven't given any opinions here today about what molecular weight a person of ordinary skill would target for copolymer-1 as of 1994, correct?

A. No, I haven't.
Q. And similarly, if we turn to slide 4. Here you have the time and temperature process limitations from claim 2 of the '898 and '430, correct?
A. Yes.
Q. And again during your direct you only focused on this limitation of these claims, correct?
A. Yes.
Q. And you found support for this limitation in the prior art, right?
A. That's correct.
Q. But you didn't apply it, you didn't give an opinion during your direct concerning the obviousness of claim 2 of the '898 or claim 2 of the '430, right?
A. That's correct, yes.
Q. If we could just turn briefly, sir, to some of the references that you did talk about, and I also want to talk about them very quickly, if we can. If you can turn to DTX 1781 in your direct binder. That was the Hayashi paper, correct, sir?
A. I never actually found that one.
Q. I just want to confirm that -- it's up on the screen and I think you confirmed with Mr. Doyle that this one actually -- well, this one doesn't mention acetic acid, correct, sir, it just mentions HBr treatment? If you could put up page 464, the

experimental section? That paragraph there. Do you see, sir, about two-thirds of the way down there's a sentence that begins the debenzylation of BLG residues?
A. He says according to the method of Idelson and Blout.
Q. But he doesn't specifically refer to acetic acid here, does he?
A. He doesn't there. I think there's another mention of this earlier in the text where he refers to the degradation. If you could pull that up so I can just check whether, it's on a later page.
Q. Here, sir, there's a reference to HBr but not acetic acid.
A. That's correct.
Q. If you could turn to DTX 1782, the Appelquist article as Mr. Doyle referred to it.
A. Sorry, I never got to these in direct, so -- 1782.
Q. Again, it's up on the screen.
A. Yes, probably the best way of doing it.
Q. I think the questions I have are fairly simple. This is not a copolymer, correct, sir?
A. No, that's true of some of the other papers, they're not copolymers, but they are polymers with a single amino acid protected, so they've all got peptide bonds.
Q. Correct, but here this is all made up of lysines, correct?
A. That's correct, but bonds, peptide bonds are closely similar.

Q. And, sir, in this paper -- because it's with lysines you're not removing a protective group from glutamic acid with the HBr acetic acid, correct?
A. That's correct, but the degradation takes place with HBr acetic acid and we don't know whether it takes place before or after benzyl cleavage.
Q. In fact, here the protecting group isn't even a benzyl as it is in copolymer-1, correct?
A. That's correct. HBr takes the carbobenzoxy group off the substrates.
Q. If we could turn to DTX 3328, please?
A. Just saying that the cleavage was accomplished by the methods of Ben-Ishai and Berger.
Q. Sir, we'll move more quickly through this if you could just focus on the questions that I ask, please. If you could turn to DTX 3328, please.
A. Okay. Yes, I have it.
Q. And this is the Blout and Idelson letter to the editor that you focused on, that you discussed in your direct, correct?
A. That's correct.
Q. This is the one, I'm sorry, that you pointed out to Mr. Doyle, that talks about HBr but doesn't actually mention acetic acid, right?
A. That's right, yes. You've got -- the closest is trifluoroacetic acid, but it's not the same. All solvents are

different from acetic acid.
Q. So this paper is not about hydrogen bromide in acetic acid?
A. That's right. You often can extrapolate from one solvent to another in many reactions.
Q. This is about a single amino acid, not a copolymer, right?
A. I didn't reference that one, but I think it came up in Dr. Zeigler's talk.
Q. This indicates that poly --
A. Which one are we talking about? This one that's on the screen?
Q. I'm sorry, MYL29820 in my binder. DTX 3328.
A. Yes. That's the paper before the one that you want to show. It's a page after. It's the second page in from that. That's it.
Q. There you go. This is not a copolymer either, right, sir?
A. No, it's a single amino acid polymer of, well, it's gamma benzyl and glutamate.
Q. Dr. Laird, you'd agree with me that it's fair to say none of the articles you've discussed on direct specifically suggested using HBr in acetic acid to cleave peptide bonds, right?
A. The article suggests using HBr acetic acid to cleave peptide bonds, but not necessarily in a polymer.
Q. Well, to be clear, the articles you've cited observed that peptide bond cleavage have sometimes occurred, right?

A. Yes.
Q. But that peptide bond cleavage is not the goal in any of the papers that you've cited, right?
A. No, but it still occurs, whether it's the goal or not. I mean, the important part of doing organic chemistry is not to look at just the reactions themselves but the side reactions, because that may lead to impurities or it may lead to something you want or it may lead to an impurity, so you have to observe those side effects. It's one of the things I've criticized some of the other papers for, that you don't follow up on what some of the reactions are. So people said you didn't get any side reaction, well, you don't know if you don't look for it.
Q. Sir, my question was much more narrow and much more straightforward. I think you agree with me, but let me make sure. You agree that none of the papers you've cited -- let me start again. You agree with me none of the papers you cited intended or were hoping the goal was to have peptide bond cleavage occur, correct?
A. That's correct, but it doesn't mean it didn't occur, so the prior art -- can I finish, please? The prior art is what it says in the literature. It doesn't matter whether you intend to do it or didn't intend to do it, you could see there's peptide cleavage.

One of the important things in Idelson and Blout is he talks about extensive peptide cleavage, so a person of skill in

the art would know if you treated something with HBr you would get some peptide cleavage. Doesn't matter what the substrate is, you get peptide cleavage.

Q. But in none of the papers you've cited, sir, was peptide cleavage intentionally controlled based on the HBr acetic acid step, correct?

A. It was not -- I'm agreeing with you. It wasn't the intention that you get some, whether it was controlled or not is not clear. It was the, as you say byproduct, unintentional, that you can use the knowledge of that peptide cleavage under those conditions to control peptide cleavage if that's what you wanted to do.

Q. But none of the papers actually discuss controlling peptide cleavage with an HBr acetic acid step, right?

A. They do not, but that doesn't mean to say you can't control peptide cleavage by a knowledge of conditions which were brought out in those papers which lead to peptide cleavage. A person skilled in the art would know you could extrapolate those conditions to get more peptide cleavage if that's what you wanted and no peptide cleavage if that's what you didn't want. Some of the papers describe, and I've mentioned one of them, Yaron and Berger, that by doing it at 2 degrees you don't get any peptide cleaving.

Q. Could we have slide 2, please from Dr. Laird's direct?

Dr. Laird, let's move on to the test reaction you discussed at

the beginning with Mr. Doyle. You put up here a slide 2 about the six claims that are asserted in this case that have the test reaction limitation, correct?

A. Correct.

Q. And just to be clear, you understand there are 22 claims asserted in this case?

A. I don't know the number. I knew it was a lot.

Q. You gave an opinion concerning infringement of these six claims, correct?

A. That's correct, because I'm sort of focusing on the process aspects because that's my expertise.

Q. Now, Dr. Laird, you looked at PTX 913 or 913R in your direct? And you don't have to turn there yet. Do you recall that document?

A. I don't. The numbers don't mean anything, but I'm sure it will when it comes up.

Q. It was the recent submission to the FDA from Sandoz. Do you recall that?

A. Okay. Yes.

Q. And that's the only process that you testified about today concerning the -- well, actually let me withdraw that. You testified about the in-process viscosity control, correct?

A. That's correct.

Q. And if you turn to page 38 of the briefing book, PTX 913, that describes that process, correct?

A. What page is that? Is that the one on the screen?
Q. Page 38.
A. I think we discussed some of the stuff in the page. I'm not sure it actually went on the screen.
Q. Now, you also talked with Mr. Doyle about batch records, correct?
A. Yes.
Q. And you're familiar with batch records from your work, right, sir?
A. Yes. I've had a lot of experience with batch records.
Q. And it's your understanding when amendments are provided to the FDA, the batch records underlying the work are also provided, correct?
A. I think that's correct, yes.
Q. Now, during your direct, you didn't talk about the actual batch record, you talked about it, but we didn't look at it, correct?
A. That's correct, yes.
Q. Could you turn to PTX 928 in your cross-examination binder? Let's take a look at the batch record, please. Mr. Chase, I think we're going to need to put this one on the private screens. It may contain some materials.
A. 928, you said?
Q. 928, please. And, Doctor Laird, let me just suggest that although you have an unredacted version of that, if you could

avoid talking about some of the particular numbers especially in the table, I think counsel for Sandoz Momenta will appreciate it.

A. Okay.

Q. Do you recognize what we've marked as PTX 928?

A. Yes, I do. It's a batch record of a particular batch assay.

MR. WIESEN: Your Honor, plaintiffs offer PTX 928 into evidence.

MR. DOYLE: No objection, your Honor, if the public record could have the redacted version. We'll work that out.

THE COURT: Thank you. Admitted.

(Plaintiff's Exhibit PTX 928 received in evidence)

Q. Now, you testified mostly about the viscometry model during your direct. Do you recall that testimony, sir?

A. Yes, I do.

Q. Are you aware the batch record has a second model, correct?

A. That's correct.

Q. Time and temperature model, right?

A. Yes.

Q. And you'd agree with me, sir, that while there are two models in the batch record, they represent one manufacturing process, right?

A. Yes. I mean, the models have been derived from slightly different sets of experiments and they are meant to be, as you

said, a viscometry measurement is supposed to be the primary method of controlling the batch, and in the event of viscometer failure or two viscometer failures then there's a backup methodology.

Q. And that's all part of the one manufacturing process that's embodied in this batch record that we've marked as PTX 928, right?

A. Yes. It's a contingency plan and the batch records that I've seen that the second 'mometer has never been used and in this particular batch record it wasn't used. It's got a line through it saying "not applicable".

Q. Again, Dr. Laird, I promise it will go more quickly if you simply answer my question. We'll get there, but if you could just listen and answer my question.

Could you turn to MMP1707035, please? Section 7.4.1?

A. I have it.

Q. Do you recognize this page, sir?

A. Yes, I do.

Q. And this is the viscometry model that you were discussing?

A. It is, yes.

Q. And if you look at the very first sentence, it indicates as you discussed on direct, while maintaining the contents of the reactor in a batch temperature of 22 plus or minus 2 degrees celsius with a target of 21.0 degrees celsius, correct?

A. That's right, yes.

Q. So that's the temperature that the Sandoz Momenta process is set at, correct?
A. That's the set temperature, yes.
Q. An your notes, sir, if you look at the table here under 7.4.4.2, I think you talked about this on direct, this table was completed based on test reactions, correct, as the Court has construed the term?
A. That's correct, yes.
MR. WIESEN: Give Mr. Chase one second. MMP1707035. Thank you.
Q. So this table that's now highlighted on the screen, Dr. Laird, and we're not going to read the numbers from it, this was created by test reactions as the Court has construed the term, correct?
A. Yes. I think it was created by experiments in a lab which would affect the change of temperature with viscosity and correlating that to molecular weight of the glatiramer acetate, so it would all be what I call standard development chemistry, but it's describing test reactions.
Q. Now, if we go up to the second bullet point above the table, and I think again this is consistent with what you explained. It reads, "In the event of the viscometer equipment failure or the inability to obtain accurate viscosity readings continue with step 7.4.5," correct?
A. That's correct, yes.

Q. That's contained in the current batch record, right?
A. Yes. It's this particular batch, so it may have changed the batch record since then, but this is what it says there.
Q. You haven't seen an updated batch record?
A. I haven't.
Q. If you turn to the next page, that's 7.4.5 correct?
A. Yes.
Q. This is what you were referring to before as the time temperature model, correct?
A. It is.
Q. You refer -- this particular batch has a slash through it?
A. That's correct.
Q. But it's contained in the batch record as a backup process, correct?
A. It is -- it's sort of a backup of a backup, because they have two viscometers and they are taking measures of two viscometers, so it seems to me as somebody who has spent a lot of time in manufacturing that it's very unusual to have a backup of a backup.
Q. And this time temperature model also has a temperature setting of 22 degrees plus or minus 2 degrees with a target of 21 degrees, correct?
A. That's correct.
Q. And the table here has an average batch temperature column, right?

A. Yes, and just point out that average batch temperature is different from the temperature we measure in the viscosity model, so you can't just measure the temperature and look across at the time. You have to do a calculation of the average batch temperature.
Q. There's an average batch temperature column on this table?
A. Yes.
Q. And there's a depolymerization time column on this table, correct?
A. That's correct.
Q. And if you go back one page again to 1707035. You see the sentence at the end of the first full paragraph says, "While the contents of the 200 gallon reactor mixes, continue with the sampling protocol in step 7.4.6," and complete some other steps, correct?
A. Yes, it says that.
Q. And you've looked at that before, too, right?
A. Yes.
Q. And if we turn to 1707038, that's the sampling protocol, correct, sir?
A. Yes, that's correct.
Q. And it shows that even during the manufacturing process, samples are taken, right?
A. That's correct, yes. I think this was one of the validation ones so you expect to take a lot of samples in

validation.
Q. This is still the up-to-date batch record as you know it, right?
A. It is.
Q. And so the current batch record includes continuing to take samples, right?
A. That's correct. That doesn't surprise me, because on my recommendation when I'm doing first phases in scaleup and early manufacture is to take samples at every possible position, because if something goes wrong later in the batch we want to know why, so it's very important to take samples all the way through production.
Q. And this page refers to taking measurements with both viscometers, correct, sir?
A. It does.
Q. And if we look at the, looks like sixth row, we see the 03 viscosity reading, correct?
A. Yes.
Q. And two rows below that is the 04 viscosity reading, correct?
A. That's correct.
Q. And if we look back we'll see the 03 is the primary viscometer, correct?
A. Yes. I think that's the long reach one and the 04 is the in line one.

Q. And the in line and the long reach viscometer don't give the same readings, right?
A. They don't, no, they're measured at different parts of the process.
Q. So you couldn't use the second viscometer as a backup for the first because they get different results, right?
A. You could if you knew what you were doing, because the in line viscometer was used originally as the primary viscometer in early batches, and so they did in fact correlate using that viscometer before they brought the long reach viscometer, so the knowledge would be there to understand that difference.
Q. So some sort of conversion would need to be done from the backup viscometer to the primary viscometer result to apply in the model?
A. I don't know exactly how we'd do it. Clearly there was data because they were using that in line, they're both in line, but the one in the recirculation loop was originally used, so there would be data around to correlate that.
Q. Whatever correlation you have to do is not in the batch record though, right, sir?
A. It's definitely not in the batch records, no.
Q. And if you go back to the viscosity model, the viscometry model and you have that table that we looked at on 1707035, do you see that?
A. Yes.

Q. You couldn't apply this table to the backup viscometer, right, because it's got a different reading?
A. I need to see what the difference is on the viscosity towards the end of the process, because from my memory it was quite a bit of discrepancy early on, but as you got towards the end of the process, the viscosities were --
Q. They get closer, right?
A. Quite closer.
Q. If you turn back to 1707035, I have one more question on this, the viscometry model page.
A. Yes.
Q. If we look at that second bullet again? Well, if we, I'm sorry, if we look at 7.4.4.1. Do you see that?
A. Yes.
Q. That has readings from the first viscometer, the 03 viscometer, right?
A. Sorry, I'm not paying attention. 7.4.4.1?
Q. You see the entries on that line?
A. Yes.
Q. And those are from the 03 viscometer, correct?
A. On 7.4.4.1 where it says "end viscosity," is that what you mean?
Q. Yes, and it specifically references the part number and that's the 03 viscometer, right?
A. Yes.

Q. And there's no reading from the 04 what you call the backup viscometer in the batch record here, correct?
A. Not on that page, but as you pointed out further on you are taking measurements with the viscometer. If I was a manufacturer, I wouldn't pay for an expensive viscometer to put in the process if I wasn't going to use the measurements that it takes. My guess is -- well, I won't guess.
Q. I just want to turn very briefly back, sir, to the briefing book, PTX 913.
A. It's in the direct.
Q. It is in the direct binder, sir. If you could look at page 37, table 15, and I think we should put this on the private monitor. That's in the redacted version. We can put that up. Putting it up. You've seen table 15 before, correct, sir?
A. Yes, I have. I haven't found it yet.
Q. It's up on the screen.
A. Let's use that.
Q. And this is what's been filed with the FDA, correct, sir?
A. As far as I know, yes. Clarifying yes.
Q. Were you here when Dr. Bishop testified that 1.1.0 is the current process that Momenta intends to use, correct?
A. I think that's what he said, yes.
Q. If you look at the last column, there's a reference to the batch record range for that process, correct?
A. Yes.

Q. One of the batch records we've just been looking at is for process 1.1.0, correct?

A. Yes, and the temperature is 22 plus or minus 2 degrees.

MR. WIESEN: Nothing further.

THE COURT: All right, Mr. Doyle.

MR. DOYLE: Very briefly.

REDIRECT EXAMINATION

BY MR. DOYLE:

Q. Dr. Laird, were you here this morning for the testimony of Dr. Bishop?

A. Yes, I was.

Q. And did you hear his testimony that Sandoz Momenta do not plan to use the time and temperature backup that's included in the batch records going forward now that the viscometer method has been validated?

A. Yes, I did.

Q. And in not testifying about the backup of time and temperature that's included in the batch record, did you rely upon that position of Sandoz and Momenta in terms of what its future plans are?

A. Yes, I did.

Q. And also, did you hear Dr. Bishop testify that with regard to revising the viscometer model further based on any sampling, that they don't have any intention to do that going forward in the future?

A. I think that's what he said. I'm sure it's in the record.
Q. And did you rely on that in not discussing that in your opinion and in your direct testimony?
A. Yes.
MR. DOYLE: Nothing further.
THE COURT: Anything else?
MR. WIESEN: No questions, your Honor.
THE COURT: Thank you, Dr. Laird, you may step down. Next witness. Who is the next witness?
MR. AANNESTAD: Your Honor if I may introduce myself again, Anders Aannestad for Sanders Momenta.
THE COURT: Yes.
MR. AANNESTAD: Our next witness is Dr. Scandella, but I was wondering if this is a good time to take our afternoon break.
THE COURT: Yes. We'll take a ten-minute break.
(Recess)

THE DEPUTY CLERK: All rise.

THE COURT: Please be seated.

Doctor, you may continue to stand, if you raise your right hand.

CARL JOHN SCANDELLA,

called as a witness by the defendant,

having been duly sworn, testified as follows:

DIRECT EXAMINATION

BY MR. AANNESTAD:

MR. AANNESTAD: Before I proceed, your Honor, I have a couple of binders. May I approach?

THE COURT: Okay.

Q. Good afternoon, Dr. Scandella.

A. Good afternoon.

Q. What is your occupation?

A. I own a consulting firm, and I provide consulting in the areas of the manufacture of new biotechnology products and the associated analytical methodology.

Q. Have you ever testified in court before?

A. No, I have not.

Q. What are your academic credentials?

A. I have a bachelors degree in chemistry from the California Institute of Technology, and a doctorate in biochemistry from Stanford University.

Q. What year did you earn your bachelors degree?

A. My bachelors degree was in 1966.
Q. Did you receive any awards when you graduated from Cal Tech?
A. Yes. I received an award as the outstanding senior chemistry major at Cal Tech.
Q. Okay. Where did you apply to graduate school after graduating your bachelors degree?
A. I applied to graduate school to the three top institutions in my field, Harvard University, the Rockefeller University here in New York, and Stanford University.
Q. And which of those institutions did you decide to go to?
A. I decided to go to Stanford.
Q. And why did you make that decision?
A. Stanford, the Stanford Department of Biochemistry was regarded at that time as the world's capital of DNA, and the chairman of the Stanford biochemistry Department Dr. Arthur Kornberg was a Nobel Laureate for his discoveries in the area of DNA, excuse me, DNA synthesis, and he was -- he was a dominant figure in the biochemistry field.
Q. And who did you work with at Stanford for your Ph.D.?
A. My thesis advisor was Dr. Arthur Kornberg.
Q. What was the subject of your Ph.D.?
A. The subject of my Ph.D. thesis was the purification and characterization of a membrane-bound phospholipase A from Escherichia coli.

Q. Who did you receive funding from for your Ph.D. research?
A. My thesis research was funded by a national science foundation predoctoral fellowship.
Q. And did that research involve the measurement of molecular weight of protein?
A. Yes, it did.
Q. What did you do -- when did you finish your Ph.D.?
A. I finished my Ph.D. in 1971.
Q. What did you do next?
A. Next I went to the Chemistry Department at Stanford to do a post-doctoral fellowship with Professor Harden McConnell.
Q. Did you receive -- who did you receive funding from for that post-doc?
A. I had a national science foundation post-doctoral fellowship for that work.
Q. What was the subject of that research?
A. The subject of that research was the measurement of lateral diffusion of phospholipids in rabbit sarcoplasmic reticulum, a biological membrane. That research was closely related to the thesis research of Dr. Roger Kornberg, who was my contemporary at Stanford, and we were both influenced by professor Arthur Kornberg to do our thesis projects in the area of cell membrane structure and molecular motions.
Q. Dr. Roger Kornberg was Dr. Arthur Kornberg's son?
A. That's right. He was Dr. Kornberg's oldest son. In a way,

the work that I did at stand in the Stanford Chemistry Department was a continuation of Roger Kornberg's thesis. Roger Kornberg won the Nobel Prize in chemistry in 2006.

Q. So both father and son won the Nobel Prize?

A. Two, two in the same family, yes.

Q. How long did your post-doc at Stanford last?

A. It was a little over a year.

Q. What did you do next?

A. After that I did a second and a third post-doc in Europe. The second post-doc was at the bio-center at the University of Basel in Switzerland, and the third post-doc was at the Pasteur Institute in Paris.

Q. What was the subject of your research at Basel?

A. The subject of my research in Basel was the molecular structure and motion of virus membrane and the cell membranes of normal and virus transformed cultured cells.

Q. Who did you receive funding from for that research?

A. That post-doctoral work was supported by the National Cystic Fibrosis Research Foundation.

Q. Was that a particularly prestigious post-doctoral fellowship?

A. It was at the time. There were only a few of them awarded, and they had a higher monetary award than other fellowships, so it was considered very prestigious.

Q. And what was the subject of your research at the Pasteur

Institute?
A. At the Pasteur Institute I worked with Professor John Pierre Changeux, one of the most famous scientists in France. Professor Changeux had developed a model for allosteric interactions for the way that protein structure changes to allow the activity of proteins to be regulated in the cell.
He was also interested in the structure and function of the nerve junction with the cell. And he was a world leader in that area, and I worked with him on the, on that area.
Q. How long did you do that research for?
A. That was a summer research project.
Q. And did your research, your post-doc at Basel, how long was that?
A. That was about two and a half years.
Q. Okay. And who funded your research at the Pasteur institute?
A. The French National Science Foundation, the acronym is DGRST, but I can't reproduce for you what that stands for.
Q. After completing your post-doctoral positions, what did you do next?
A. After my post-doctoral positions, I became an assistant professor of biochemistry here at State University of New York at Stony Brook.
Q. How long were you in that position?
A. I was there for seven years.

Q. Did you teach courses?
A. Yes, I taught a number of courses at Stony Brook, including biochemistry for undergraduate, graduate and medical students. I also taught the regulation of metabolism for graduate students, physical biochemistry, and my special area of interest was cell membranes. I taught a course in cell membranes.
Q. Did you run a research laboratory at Stony Brook as well?
A. Yes, I did.
Q. What was the subject of that research?
A. The subject of that research was an extension of the work that I had done in Basel and Paris and my chemistry post-doc at Stanford. It was using magnetic resonance to study the membranes of sea urchin eggs after they've been -- before and after they've been fertilized to understand the changes that take place in the egg's membrane when it's fertilized.
Q. Was that research on the molecular level?
A. Yes, that's correct.
Q. Did you receive any funding for that research?
A. Yes. That research was funded by research grants from the National Institutes of Health and the National Science Foundation and other sources.
Q. Have you served in any academic roles, more recently?
A. Yes. I've continued to be involved in academics. Since I moved to Seattle area, I've been active at the University of

Washington, where I've taught a course for about ten years in pharmaceutical biotechnology, and also I've been active in a major research institute in Basel called the Institute for Systems Biology.

Q. And does your teaching in the pharmaceutical biotechnology course include size exclusion chromatography?

A. Yes, it has.

Q. And did your teaching at Stony Brook involve size exclusion chromatography?

A. It involved physical techniques for studying molecules. Size exclusion was one of them, yes, but there were many others.

Q. After leaving Stony Brook, what year was that?

A. That was in 1981.

Q. Okay. What did you do next?

A. In 1981 I joined the biotechnology industry. The industry was just getting going at that time, and a number of my friends and colleagues from graduate school had made the switch from academia to the biotech industry, and there were very exciting frontiers on that industry, in that industry, but not many products had come out of it. So I wanted to participate in the creation of new products using biotechnology.

Q. What is the first company you went to work for?

A. The first company I went to work for was Genex Corporation in Rockville, Maryland.

Q. What did you do there?
A. At Genex I was a principal scientist in protein chemistry, and I worked on the solubilizing and refolding of recombinant proteins. At that time it was known that most proteins that were expressed in ecoli were expressed in an insoluble inactive form, and a fronter was finding ways to restore those proteins to activity. I discovered and patented one of the early methods for doing that.
Q. When did you leave Genex?
A. I left Genex in 1983.
Q. Where did you go?
A. From Genex, I went across country industry to Emeryville, California near Berkeley, and joined a company, start-up company called Chiron Corporation.
Q. How big was Chiron at the time you joined?
A. Chiron had about 50 employees when I joined them in 1983.
Q. If you could describe, generally, some of the projects that you worked on at Chiron?
A. I worked on four major products, projects at Chiron. All of them turned out successfully and all of them contributed to Chiron's success.

The first project was insulin like growth factor 1, or IGF-1 as it called. That was the highest priority at Chiron for much of -- the highest priority project at Chiron for much of the time that I was there, because it was the initial

project in the collaboration with Ciba-Geigy, the large Swiss pharmaceutical company, and Chiron wanted to use Ciba-Geigy as a springboard to become a larger company.

Q. And what was the next project you worked on?

A. The next project I worked on was superoxide dismutase. Superoxide dismutase is a protein that attacks or disintegrates the superoxide and ion, and it was interest -- of interest to Chiron for a couple of reasons.

For one reason, it was, it was the proof of concept protein to prove Chiron's technology for making human proteins in yeast cells. Prior to that, most proteins were made in ecoli. And baker's yeast has considerable advantages as a production organism over ecoli.

So the superoxide dismutase project was, on the one hand, a demonstration of our technology and, on the other hand, it was an interesting, interesting as a potential pharmaceutical product in its own right.

Chiron was able to establish partnerships with two major pharmaceutical companies to develop superoxide dismutase, and it was also the basis of a partnership with Pharmacia that we'll talk about later.

Q. In addition to Pharmacia, what were the other companies that Chiron partnered with?

A. I, as I said, IGF-1 was partnered with Ciba-Geigy; superoxide dismutase was partnered words with Gruenenthal in

Germany, and Pharmacia in Sweden.

The GP-120 project, HIV GP-120 project that I worked on was a key project in developing diagnostic tests for AIDS, and also in developing candidate vaccines for AIDS. Ciba-Geigy also became a partner with us for that project, and they supported the development of a vaccine business by Chiron called Chiron vaccines.

The fourth project, and probably the most important project both for Chiron and this case was the Hepatitis C virus project at Chiron. Chiron discovered, discovered the Hepatitis C virus, the agent that cause, that caused the disease that previously had been known as Non A- Non B Hepatitis. This is a disease that spread through the blood supply. Prior to Chiron's work, anyone receiving a blood transfusion in the United States or most of the civilized world, had a 15 percent chance of contracting Hepatitis C. There was, there was no known no effective test for that. Through Chiron's work, we found an -- we were able to clone an antigen that contained sequences from the Hepatitis C virus, and that antigen was used at Chiron to create a diagnostic product. The role of my group in that project was to develop a size exclusion chromatography step for that, for that antigen. It was a very difficult protein to analyze. And the most effective step was size exclusion chromatography. And my group was the size exclusion chromatography expert group in Chiron. So the whole company

worked on that project, and the particular part that my group played was to develop the size exclusion step as a preparative step for the purification of the antigen, and also as an analytical assay for use in the project. My group spent more than a year doing nothing but size exclusion chromatography for that project.

Q. And before we get more into size exclusion chromatography, how successful were these projects at Chiron?

A. Well, I would say they were extremely successful. All four of the projects that I worked on achieved their objectives. As I've said, the Hepatitis C diagnostic test was partnered with the Ortho Division of Johnson & Johnson. It had sales of a billion dollar range, and that test, that product alone made Chiron a profitable company.

Other products that were developed at Chiron included the first recombinant vaccine, recombinax that was done in collaboration with Merck. And the betaseron product that we heard about earlier, that we heard about last week was also a Chiron product. The (phonetic) Pearl Loopman product was also a Chiron product, and the IGF project, and the superoxide dismutase project were still continuing when I left Chiron.

Q. Were you promoted during your time at Chiron?

A. Excuse me. Yes, I was promoted to the highest scientific level at Chiron.

Q. And when did you leave Chiron?

A. I left Chiron in 1992.

Q. How large is Chiron when you left?

A. When I left, Chiron had 2,000 employees.

Q. What was your experience with size exclusion chromatography at Chiron?

A. Well, size exclusion chromatography was used in every project that I did at Chiron, and there were different ways. As I've said, in the Hepatitis C project, it was it was the main protein purification tool for purifying the antigen that was used to make the diagnostic product.

I used, I used size exclusion chromatography in every project that I did going back to my Genex work in recombinant protein folding and refolding.

Size exclusion chromatography uniquely tells you information about what a protein is doing in solution; if it's folding or unfolding, if it's denaturing, if it's aggregating. Size exclusion chromatography is used as a release test for nearly all recombinant pharmaceuticals. Because the FDA is very concerned about the formation of aggregates in protein products. Aggregates tend to be more immunogenic. So nearly every protein product has a size exclusion step as part of the stability indicating assay and as part of the release method that's used for the product.

Q. How many different size exclusion chromatography columns did you use at Chiron in terms of category or brand?

A. Well, I had a, I had a drawer full of size exclusion chromatography columns and when I became a consultant for Pharmacia, they supplied my laboratory with chromatography columns. So I had a large number of columns. And in my laboratory I had six analytical instruments that were going pretty much constantly as ways to monitor our different products. And at least one of these was always set up for size exclusion chromatography. And in some cases it was three or four of them were running.

So I had an analytical machine in my laboratory at Chiron, and I could run thousands of samples very quickly. I would estimate that I ran at least 10,000 size exclusion runs, although I never actually kept count of that.

Q. During your time at Chiron, were you recognized by the maker of the Superose 12 column as an expert in SEC?

A. Yes, I was. The Superose column, 12 column is made by Pharmacia, a Swedish company based in Uppsala, Sweden. And I first became acquainted with Pharmacia because of our partnership with on the superoxide dismutase project, and they quickly recognized that I was a large scale user on high profile projects with size exclusion chromatography. So they asked me to serve as a beta, my lab to serve as a beta test site for their newest generation size exclusion chromatography, which at that time was Superdex 200.

Q. What does that mean to be a beta test site?

A. Well, it means that I tested the size exclusion columns from Pharmacia and compared them to the other columns that I used in my laboratory. I provided this information back to Pharmacia, and it was used in promotional literature, and it was also used as the basis for a course that I then taught with Pharmacia.

Q. Can you describe that course?

A. Yes. Pharmacia has been a leader in protein purification technologies for many years. They make the columns and the instruments that are used for that purpose, but they also teach a series of courses around column chromatography technology. And at the time, at that time they wanted to add a course in purification of recombinant proteins to there repertoire and they asked me if I would help them design and teach the course.

Q. And how many years did you do that?

A. The course was first offered in Freiburg, Germany, I believe it was in 1989, and I taught the course several times, the last time being in Tokyo, which I believe was in 1991. This was a lecture and laboratory course. And the laboratory portion of the course was based on purification of superoxide dismutase. My company, Chiron, provided the crude superoxide dismutase, the starting material that we used for purification in the lab course.

Q. In what way does the Superdex 200 column that you were talking about differ from the Superose 12 column?

A. Well, the Superdex 200 column was a newer generation. The Superdex 200 column had beads that were more rigid. They would withstand higher pressures and higher flow rates, and it was clearly superior as a preparative medium, and also had advantages as an analytical medium.

Q. Was that a usual practice at Chiron to allow its employees to consult for other companies?

A. No, it was not usual. In fact, Chiron had a policy of not allowing its employees to consult for for-profit companies. They made an exception in this case, partly because Pharmacia was their partner, and partly because they considered it was an honor that a Chiron employee would be asked to consult in purification for Pharmacia, which was considered a world leader in purification at that time.

Q. Why did you originally begin using size exclusion chromatography in your research?

A. Well, I recognize -- excuse me. I recognized from my work at Genex where I was working -- excuse me -- in my work at Genex on refolding a recombinant protein, I recognized that size exclusion chromatography had unique advantages in being able to tell me about what the molecule was doing in solution. There were other techniques for measuring molecular weight, but size exclusion chromatography was unique in being a simple technique for watching what the molecule I was working on was doing in solution. And I used that as a, routinely as a tool

in all of my projects afterwards. And I believe it was one of the keys for the success that I had.

Q. Did you personally operate the SEC column during your time at Chiron?

A. Yes, I did. I was a hands-on scientist. I had administrative responsibilities as the head of the process development group, and the head of the protein manufacturing group at Chiron. But, frankly, I loved to work in the lab. And size exclusion chromatography was my favorite thing because it was an intellectual game.

As you I think you're going to see as we get into this case, size exclusion chromatography experiment has to be properly designed if it's going to give you the result that you want. And I enjoyed the intellectual game of designing the size exclusion chromatography experiments.

Q. Does your work today still involve size exclusion chromatography?

A. My work where?

Q. Your work today?

A. Yes. I've used size exclusion chromatography throughout my consulting career. In some projects it's a major component, in some projects it's a minor component, but it's always there for the reasons that I outlined earlier.

Q. In addition to Pharmacia, what companies have you consulted for?

A. Well, I think I've consulted for 44 companies at this point, and they've covered a range. They're not all the same.

Many of my consulting clients have been young biotechnology companies that were trying to manufacture their first product for clinical trials. I've also worked for analytical laboratory services, I've worked for law firms. There's been a range, but that's what's most typical.

Q. Did your use of size exclusion chromotography at Chiron include the measurement of molecular weight?

A. Oh, yes. Size exclusion chromotography is interesting in that regard. When I use size exclusion chromotography, I would always run standards, and I was always measured the molecular weight of the substance that I was interested in.

But the size exclusion chromatogram contains more information than just the molecular weight. And recombinant proteins tend to do strange things in solution, that's -- it's kind of their habit. And I use size exclusion chromotography to stay on top of that.

Q. Have you developed reference standards that have been adopted by any government agencies?

A. Yes, I have. For each of the projects that I worked on at Chiron, there was no reference standard available when I started working in the project. So, for example, in the IGF-1 project, we developed a reference standard and characterized the reference standard, and it was accepted as a reference

material by the World Health Organization.
Q. Has NIH adopted any of your standards?
A. Yes. Another of the standards that were created in my group was adopted by the National Institutes of Health as an AIDS reference reagent.

The GP-120 protein that I worked on, the protein that's on the outer surface of the AIDS virus, was the focus of a lot of work that's been done on developing diagnostic tests for AIDS, and also vaccines for AIDS. And we were able to develop a superior version of the GP-120 protein at Chiron, and we patented that material, and we also published on that material. And that, that protein was adopted as a standard by the Institutes of Health in the United States and the PDRP in Europe.
Q. What year was that?
A. That was around 1990.
Q. Dr. Scandella, do you have experience characterizing the molecular weight of proteins using analytical techniques, other than SEC?
A. Yes. I've used a range of analytical techniques to characterize protein molecular weights. The molecular weight of a protein is the most fundamental parameter that describes that protein. And for every project, it was necessary to establish the molecular weight, and that was usually done by applying multiple methods.

Q. Which analytical techniques have you used for that?
A. I've used analytical ultracentrifugation, I've used mass spectrometry, maldi-tof spectrometry, electrospray mass spectrometry, kutov mass spectrometry. There have been a number of them.
Q. Have you used maldi-tof?
A. Yes, I have.
Q. Viscosity?
A. I've used viscosity, but not for the measurement of molecular weight.
Q. Have you used light scattering?
A. Yes, I've used light scattering also.
Q. And are you familiar with the principles underlying ionometry?
A. Yes.
Q. Do you have experience in characterizing the molecular weight of polypeptides with analytical techniques other than SEC?
A. Well, proteins are polypeptides, so every protein that I worked on has been a polypeptide.

In addition, I've worked on a number of polypeptides that were created by recombinant DNA technology, but were not proteins. They were genetically engineered polypeptides. And I've also worked on insulin and insulin derivatives that were not poly -- not naturally occurring.

Q. Have you written articles published in peer-reviewed journals that included the use of size exclusion chromotography?
A. Yes, I have.
Q. And I want to make sure we covered this. We'll be discussing the 1987 to 1994 timeframe a lot during your testimony.
Did you give any presentations regarding Pharmacia's size exclusion chromotography columns during that time period?
A. Yes, I did. I gave a presentation in 1989 at a recombinant protein meeting in Interlaken, Switzerland, at which I included this information.
Q. Okay. Who asked you to present there?
A. The organizer, organizer of the meeting were some Swiss scientists from Basel, and I was asked by them to present this information.
Q. Are you active in any professional organizations?
A. I'm a member of the American Chemical Society, and the American Association of Pharmaceutical Chemists. And I've participated in, as I've said before, in activities at the University of Washington and the Institute for Systems Biology in Seattle.
Q. What is the Institute for Systems Biology?
A. The Institute for Systems Biology is interesting. It's a world leader in the development of new technology for solving

bio-medical problems. It was founded by Dr. Leroy Hood who is one of the leaders in the biotechnology industry. Dr. Hood was the founder of Amgen Applied Biosystems, a major instrument manufacturer, and about 15 other companies. And he was brought to Seattle in 1993 by the University of Washington with the help of a $13 million grant from Bill Gates. He's been a dominant figure in this field. And in 2000 he founded the Institute for Systems Biology in Seattle, and it's now a world renowned institution.

Q. Thank you. And, Dr. Scandella, without forcing you to cover the technology you've already described, are you the inventor on any patents?

A. Yes, I am.

Q. Okay. In which fields?

A. All of my patents are in the field of protein technology and in solubilization of refolding and purification. And the GP-120 patent includes protein purification technology, but it's about how we developed this superior GP-120 antigen and tested it in baboons, cats, different animals, to arrive at a better antigen.

Q. And, Dr. Scandella, you've already mentioned Dr, the Doctors Kornberg before today. But have you had the privilege of learning from and working with any other Nobel Laureates during your career?

A. Yes, I have. I've been very fortunate in my education and

career, in that I've had eight Nobel Laureates either as teachers or collaborators, and I've also had a number of other outstanding scientists who aren't Nobel Laureates, but are very widely known also.

Q. Dr. Scandella, could you please turn to DTX-3564 in your binder?

A. Yes, I have it.

Q. Is this a current copy of your CV?

A. Yes, it is.

MR. AANNESTAD: Your Honor, we move for the admission of DTX-3564.

MR. JAMES: No objection.

THE COURT: Admitted.

(Defendant's Exhibit 3564 received in evidence)

MR. AANNESTAD: Could we please put on the screen paragraph 47 from Dr. Scandella's report on the level of skill in the art?

Q. Dr. Scandella, is this the definition of a person of ordinary skill in the art apply for your opinions in this case?

A. Yes, it is.

Q. Do you consider yourself as having been a person of at least ordinary skill in the art in 1994?

A. Yes, I do.

Q. And do you consider yourself as having been at least a person of ordinary skill in the art in 1995?

A. Yes.
Q. Were you present in court for Dr. Grant's testimony last week?
A. Yes, I was.
Q. And have you reviewed the testimony of Dr. Owens?
A. Yes, I have.
Q. Were you here for the testimony of Dr. Bishop today?
A. Yes.
MR. AANNESTAD: Your Honor, we offer Dr. Scandella as an expert in the use of size exclusion chromotography and the characterization of molecular weight.
THE COURT: Any objection?
MR. JAMES: No objection.
THE COURT: All right. Court accepts you as an expert in those fields.
Okay, go ahead.
MR. AANNESTAD: Thank you, your Honor.
Put up slide one, please.
Q. Dr. Scandella, is this a summary of the topics you would like to cover?
A. That's right.
Q. Let's start with molecular weight, slide two.
What is your understanding of the term "molecular weight"?
A. Well, molecular weight is a basic concept in chemistry. If

one has a chemical structure, the molecular weight is the sum of the atomic weights of all of the atoms in that structure. For a molecule like cop-1, that definition isn't useful because we have -- first of all, we don't know the structure, and, secondly, we have no way of measuring the molecular weight.

Q. And is molecular weight calculated or measured?

A. Well, if one knows the structure, it can be calculated and measured. If one doesn't know the structure, then it has to be measured.

Q. What is average molecular weight?

A. Well, there are several kinds of average molecular weight. But in every day terms, the most common type of molecular weight number -- number average molecular weight has the same meaning that any other parameter does. If you were to say what's the average weight of all of the people in this room, we would ask each, ask each of the people to stand on the scale.

THE COURT: I'm not joining that group.

MR. AANNESTAD: Neither am I.

Q. Okay. Is there a difference between the meaning of average molecular weight for a complex than for a simple molecule?

A. Yes. As an experiment, there's a big difference. For a simple molecule, there are a number of methods that could be used to measure molecular weight, and they would probably all give the right answer.

For a complex molecule, such as we're talking about in

this case of cop-1, there's actually no method known that, that will definitely give the right answer.

There are a few methods that are called absolute methods that will -- that can or are capable of giving the right answer, but that doesn't mean they will give the right answer in every case.

So for a large complicated molecule like cop-1, the meaning of molecular weight becomes fuzzy. One has to specify what method one is going to use to measure molecular weight, because different methods will give you different answer, as is seen in the cop-1 case.

Q. And you've mentioned cop-1 a couple of times. In what capacity are you familiar with copolymer-1?

A. I'm familiar with copolymer-1 as an expert witness in this case. I was asked to review the Teva documents relating to this, and that's what I've done.

Q. Did you work with copolymer-1 before your work on this case?

A. No. Copolymer-1 was not available commercially until after 1995, and neither I nor anyone else had, except Teva, had experience with copolymer-1 at that time.

Q. How long have you been working on this case?

A. Almost two years.

Q. Do you believe that the molecular weight of copolymer-1 should be treated as an average molecular weight?

A. Yes, I believe it has to be treated as an average molecular weight.

Q. Why is that?

A. For the reasons that I stated, that we don't know the chemical structure of the individual atoms or the individual molecules that make up cop-1, and so we can't simply calculate based on the chemical structure. And there is no way, even in principle, to measure each of the -- to measure the molecular weight of each of the molecules by mass spectrometry, for example. So we have to deal with the average with the collection of cop-1 molecules.

Q. Are you familiar with the number of possible different sequences in a sample of copolymer-1?

A. This is an interesting point, that the -- because of the size of copolymer-1, and the fact that there are many possible, possible monomers at each position of the chain, and there is around 70 positions, the number of possible sequences of cop-1 is -- I've heard the number ten to the 29th, and that's an incredible number. None of us has any experience with a number that big. Chemists like to think in materials of a mole of something, but a mole of something is about ten to the 23rd, and that's still a million times smaller than ten to the 29th. And I've heard that the number of stars in the universe is ten to the 22nd, and that's ten million times smaller than the number of cop-1 molecules calculated -- number of cop-1

structures calculated.

So we're dealing with an incredibly large number of. And, for all practical purposes, it's an infinite number. There's nothing we can do to make this, this large number of molecules countable or measurable individually.

Q. Are there different types of average molecular weight?

A. Yes, there are.

Q. What are they?

A. The most commonly used types of average are number average, weight average, Z-average, and sometimes people use viscosity average, which is still another kind.

Q. What about peak molecular weight?

A. Well, in my opinion, the term peak molecular weight describes a single point on the chromatogram, and not -- so it's not a true average. It's just where the peak occurs. It has been used as so-called peak average in the Teva literature, and in the reports that have gone back and forth about this molecule. But, in my opinion, it is not a true, not a true average.

MR. JAMES: Your Honor, I think what we're talking about here is claim construction again. And as your Honor knows, we've had two hearings on that and your Honor's rendered a claim construction order. So I would just object to testimony that's just going back to rehash the claim construction issues.

MR. AANNESTAD: Your Honor, we're not trying to rehash construction issues. He's going to be talking about these values during the day, and that's the only question on it and I just want to be clear for the record.

THE COURT: All right. Go ahead. That's fine.

MR. AANNESTAD: If we could put up slide three, please.

Q. Is this a slide you helped prepare?

A. Yes, it is.

Q. What does this show?

A. Well, the purpose of this slide is to illustrate that for a particular sample of a copolymer -- we were calling it sample A in this test tube -- there are several molecular weight averages that can be associated with that polymer. And on the top I've shown the number average, the viscosity average, the weight average, and the Z-average, and underneath I've indicated the peak average for the reason that I explained.

Q. For a given sample with a distribution of molecular weights, are the different types of molecular weights typically the same?

A. Well, unless the molecule is a single species, the different types of averages will be different, the numerical value will be different.

Q. What is the general relationship among the different types of molecular weights for complex polymers?

A. By their definition, the number average is the lowest, the weight average is larger than the number average but smaller than the Z-average, and the Z-average is the highest.

The viscosity average is somewhere -- it may be close to the weight average or maybe not. And the peak average doesn't bear a definite relationship to these, but it's often it's usually between the number average and the weight average.

Q. Will different analytical techniques yield different types of average molecular weight?

A. Well, in principle, they would all yield the same value. But when you get into this region of very complicated samples, they often don't yield the same value. And as we're going to see later for cop-a, they don't yield the same value -- cop-1. Excuse me.

Q. What are the various types of molecular weights that you can get from size exclusion chromatography?

A. One can get number average, weight average, and Z-average from -- and peak average from size exclusion chromotography.

MR. AANNESTAD: Could we move to the next slide.

Q. I like to talk to you about a little bit more about size exclusion chromotography or SEC.

We've heard a lot about SEC in this trial. Could you please describe how it works in your own words?

MR. AANNESTAD: And, your Honor, if I may approach the witness, I have -- Dr. Scandella had requested for this he

could use the Superose 12 column that we have.

THE COURT: Sure.

Q. Could you please describe in your words, briefly -- we don't need the full lecture -- but that you would be able to describe it in your words, please?

A. This is, this is a sample of the Superose 12 column produced by Pharmacia that was used in the analyses that we're discussing in this case.

It's an analytical column. And at the top one injects a sample of protein or copolymer-1. And the sample might be in a volume say of 100 microliters, 10th of a milliliter. There's a pump that pumps the mobil phase through the column, and it sweeps the sample down this column. The column is packed with tiny beads that are the Superose 12 material, and the beads have pores in them so that -- so that the small molecules can penetrate into the pores and see a relatively large volume. And the large molecules can't get into the pores. So the large molecules will come out this column first, and the small molecules will trail behind. And this is the basic principle of size exclusion chromatography.

Q. Thank you.

MR. AANNESTAD: If we could have the next demonstrative, please.

Q. What are we looking at here, Dr. Scandella?

A. This is a chromatogram for my work. It depicts the size

exclusion chromatogram of a large and complicated glyco protein, a protein called myeloperoxidase. This is the one of the projects that I worked on. And we use size exclusion chromotography, along with mass spectrometry and other techniques to characterize this protein.

Q. This is not copolymer-1, correct?

A. No, this is not copolymer-1. Copolymer-1 would give a much broader peak than this. This is, this is a broad peak compared to most proteins. Because this molecule has carbohydrate residues attached to the protein backbone, and the carbohydrate residues are of a variable structure. So this is a complicated molecule too. It has thousands or probably millions of different forms, but it's not nearly as complicated as cop-1.

Q. And what's shown along the bottom, the X axis on this chromatogram?

A. The X axis in this figure and in most size exclusion chromotography figures is time. We have zero minutes on the left side, and 16 minutes on the right side, and there's two minute increments along the X axis.

Q. Is that referred to as retention time?

A. This is referred to as retention time, that's correct.

Q. What factors control the retention time of a material passing through a SEC column?

A. One factor is the molecular weight. Another factor is the molecular shape. They both influence the retention time.

Q. Are there other factors that influence the retention time?
A. Yes. If there are any interaction between the column matrix and the sample, for example, ion exchange interactions, then that will influence the retention time also.
Q. What are the range of possible shapes that a protein or polypeptide could have in an SEC column?
A. Well, there's a wide range of possibilities. My freshman chemistry professor Linus Pauly taught me and the rest of the world about the fact that polypeptides can form alpha helix sheets, beta helix sheets, beta pleated sheets. There are a number of possible structures that a polypeptide chain can form, and it's very difficult to predict what structure polypeptide is going to have at any time.
Q. In your opinion, are the copolymer-1 molecules in an SEC column likely to adopt more than a single shape?
A. Well, it's almost certain that they adopt more than a single shape, because they have so many different conformations.
Q. How many potential different shapes are there?
A. A large number.
Q. There as many different potential shapes as there are molecules?
A. I should qualify that. We're talking about the second, here about what's called the secondary structure of a polypeptide. The tendency of the polypeptide backbone to form

helix sheets, pleated and beta pleated sheets and so forth is called the secondary structure. But there can also be tertiary structure beyond the alpha helix beta sheet structure, where the folding of the chain now takes a definite shape. So that's called tertiary structure. And copolymer-1 can and apparently does have tertiary structure, as well as secondary structure.

Q. Have you reviewed data in this case regarding which shapes copolymer-1 adopts in solution?

A. Yes, I have.

Q. If you could please turn to DTX-1113 in your binder. Have you seen this document before? I'll give you a minute to get there. It's DTX-1113.

A. I don't see that in my binder. Am I missing --

Q. I think it might be the first one?

A. Oh, yes. Sorry. Okay.

Q. Do you have an unredacted version of that there?

A. My binder has a redacted version.

Q. Behind the redacted one, you have an unredacted one? Maybe it has a colored sheet between it?

A. Oh, yes. Here it is. Okay.

Q. Have you seen this document before?

A. Yes, I have.

Q. What is it?

A. It's a description of copolymer-1. I believe it's from Teva's NDA submitted to the FDA. It's a description of the

drug substance.

In the pharmaceutical industry, one distinguishes the active ingredient of a drug as the drug substance, and the finished drug product that what's delivered to the patient is called the drug product.

Q. And this is from Teva's NDA for copolymer-1?

A. Yes. This is the description of the drug substance.

Q. If you could turn to the page ending with the TEV number ending 034, please?

A. Yes.

Q. Does this document contain information on the structure of copolymer-1?

A. Yes, it does.

Q. Okay. What information does it contain?

A. It describes circular dichroism and fourier transform infrared spectroscopy results, which are ways of detecting secondary structure in a polypeptide. And it says that a non-random distribution of helicity was found, and the alpha helical confirmation of cop-1 is a stable one. And it says in the first sentence, it says there is a relatively high alpha helical conformation, in parentheses secondary structure of cop-1.

Q. What is an alpha helical conformation?

A. Well, the alpha helical conformation is the ordered structure of the polypeptide backbone. It's not talking about

the side chains of the protein. It's talking about the peptide bond and how the peptide bond is ordered in for one amino acid relative to the next amino acid in the chain. And for an alpha helix, that's a helical structure.

(Continued on next page)

Q. What conclusion do you draw from this data that Teva submitted to the FDA?

A. I conclude that cop-1 has a relatively high alpha helical conformation. It is not a random coil.

Q. Did you have a demonstrative prepared showing different possible structures of copolymer-1?

A. Yes, I did.

Q. Slide 6, please.

A. There are six panels in this slide. The upper left panel shows schematically what a random coil might look like, and here we're not intending to imply any particular structure, but just that the polypeptide backbone meanders with no particular structure in solution.

The second panel in the middle shows the alpha helical conformation. The lower left hand panel shows the rod-like cop formation. The lower middle panel shows the beta pleated sheet and if you look closely, it may be hard for you from where you're sitting, but if you look closely the beta pleated sheet on the left side has parallel arrows, that is, the chains are moving in the same direction, whereas the beta pleated sheet on the right side has antiparallel arrows, every other chain reverses its sets. So these are the main possibilities that one would consider.

And if we combine this simple picture with the information that we just discussed, we would say that the cop-1

molecule probably looks something like the cartoon shown in the upper right-hand corner, that is, some parts of it are helical and some parts are random coil.

Q. Would a person of ordinary skill in the art in 1994 have known which of these shapes copolymer-1 would assume in solution?

A. No, one can't predict, unfortunately, the shape of a polypeptide chain. One has to determine it experimentally.

Q. And how would one do that?

A. Well, there are different ways of doing that. One way of doing that is to run that on a calibrated size exclusion column, and if one knows the molecular weight, then one can tell whether the molecular weight corresponds to the molecular weight expected from the calibration standards used.

Q. How do the different possible shapes of copolymer-1 in solution impact the determination of molecular weight with SEC?

A. Well, they're absolutely critical for the determination of molecular weight by SEC, because the SEC technique is so sensitive to molecular shape.

Q. Generally speaking, is molecular weight measured or estimated with an SEC analysis?

A. The SEC technique is not an absolute technique. It never gives an absolute number. This is well known in the field. Depending on how well it's calibrated, it could be close to the absolute value if the absolute value is known, or it could be

quite far off.

Because of this shape problem, the molecular weight measured for an unknown sample can be off by tenfold or more if the shape of that sample doesn't agree with the shape of the standards that were used to create the standard curve for the column. SEC is usually used in a relative mode, where one selects a set of standards and measures the molecular weight relative to those standards and states that the molecular weight is relative to the standards. The task of creating standards that match a sample as complicated as cop-1 is quite difficult and takes years.

Q. Is it correct to say that when determining molecular weight with SEC it's always an estimate?

A. Yes. Normally SEC values are referred to as estimates.

Q. How does one determine the molecular weights of calibration standards that are to be used with an SEC molecular weight experiment?

A. Well, that's an interesting question and a lot of work has been devoted to that topic. The short answer is there are a number of possibilities and it's not clear which way to go. One could adopt several different ways of calibrating the column.

Q. Is it necessary to know the molecular weights of your standards before they can be used for SEC?

A. Well, if you want to use the column to create a calibration

curve for the measure of molecular weight, yes, you need to know the molecular weight of the standards.

Q. What are some of the methods that can be used for that purpose?

A. A variety of methods could be used for that purpose and have been used for that purpose. In general, one can use viscometry, light scattering mass spectrometry, any number of things. In this case, there are no easy ways to measure the molecular weight of cop-1, so the creation of self standards is a considerable task.

We have a chicken and egg problem here. We want to use the size exclusion column to measure the molecular weight of cop-1, but if we don't have any characterized standards of cop-1, you're out of luck, because SEC can't do that. You then have to go to another method, another molecular weight method.

Q. And are all those techniques that you mentioned called absolute methods?

A. No. There are only a few physical methods that are capable of giving absolute molecular weights, and SEC is not one of them.

Q. But the other methods, the other analytical methods, are those termed as absolute methods?

A. Yes. There are -- mass spectrometry is considered an absolute method, osmometry is considered an absolute method, sediment, ultracentrifugation is considered an absolute method.

Light scattering is considered an absolute method, but that doesn't mean that every measurement by all of these techniques gives you a true molecular weight. All of these methods are subject to limitations and complication, especially when dealing with complex molecules.

Q. Like copolymer-1?

A. Like copolymer-1.

Q. What do you base that opinion on?

A. I base that opinion on my years of experience characterizing proteins.

Q. Do you base it on anything else?

A. Could you state the question again?

Q. Have you also reviewed Teva documents in this case?

A. Yes, I have reviewed almost ten years worth of Teva documents in this case, and of course, in a case like this, the real experts are the scientists in the company where the product is developed, and my opinion is guided to a large extent by what happened and what the Teva scientists have reported.

MR. JAMES: Your Honor, if I could be heard on this just for a moment? As you know, early in this case the defendants moved to strike the testimony or the declarations of Dr. Dubin and Dr. Grant under Daubert, and they were in part, the motion was based in part on the fact that Dr. Grant and Dr. Dubin had not looked at what Teva actually did, at Teva's

actual work, the underlying work, and your Honor in denying that motion said that what Teva actually did in order to determine the molecular weight was not relevant to the opinions of Dr. Dubin and Dr. Grant. You said, "It is beyond dispute that a person of ordinary skill in the art such as Dr. Grant and Dr. Dubin, a point unchallenged by defendants, would not have had access to Teva's internal documents and in fact because neither expert refers back to what Teva actually did, both opinions carry a greater degree of objectivity than they would otherwise if they did refer to what Teva actually did."

And we believe, your Honor, that what we're talking about here today is indefiniteness and enablement, again, the same things your Honor was dealing with then and we don't think that relying on what Teva did for the years it was developing Copaxone is relevant to this analysis.

THE COURT: You may be right, but I'm going to listen to it.

MR. JAMES: Thank you, your Honor.

THE COURT: Okay. I'm a little surprised at the way this case has been presented from the beginning, frankly.

MR. AANNESTAD: Your Honor, thank you for hearing the testimony. I'm a little bit surprised to hear this, they haven't raised this suggestion before. And Teva has put at issue in this case what Momenta did to determine the molecular weight, what Mylan did to determine the molecular weight,

so it's pretty surprising.

THE COURT: You won, Mr. Aannestad, so keep going.

MR. AANNESTAD: Thank you.

Q. Dr. Scandella, why don't you use SEC to measure the molecular weight of the calibration standards?

A. For the reasons that I outlined a moment ago, that SEC is not an absolute measurement of molecular weight. It has to be calibrated with something that has the same shape, the same ratio of hydrodynamic volume to molecular weight as the sample being analyzed, so one needs a calibration curve based on molecules of cop-1 or something very much like cop-1 that has the same shape to the molecular weight relationship and that doesn't exist. And the analytical methods that can be used to measure the molecular weight of the cop-1 standards are not up to the task. Teva struggled with this. Anyone of skill in the art -- I've been involved in doing similar measurements to this myself and I know that you run out of analytical capability. Even though we have an enormous array of powerful analytical techniques, there are samples that are beyond what can be handled with the technology we have, and that's the case here.

Q. I understand you prepared a couple of demonstratives regarding how calibration curves are constructed and could impact the molecular weight result attained. Is this the first one of those?

A. Yes. This slide after Dr. Grant's figure is an

illustration of how one makes a calibration curve for an SEC column, and how one applies that calibration curve to obtain molecular weight values for a polymer such as cop-1.

The sharp peaks in the middle of the figure represent five different standards of different known molecular weights that have been run on the SEC column, and each of them gives a sharp peak and there's a retention time associated with each peak and a known molecular weight associated with each peak. And again, the molecular weights must come from some other method. They didn't come from an SEC measurement.

So one first runs the standards as we've indicated in the middle figure, and then one plots the retention time for each peak against the logarithm of the molecular weight known for that peak. So the bottom panel shows the calibration curve, which is constructed from the elution times and the known molecular weights for the standards. So we have five data points on this standard curve and we've drawn a straight line through the data points. So that's the calibration part of SEC.

And then the way one uses that calibration is shown in the top slide.

Q. If you could use your laser pointer? I want to remind you of that, if that would be helpful. Do you have your laser pointer there?

A. Yes. So these are the samples of the known molecular

weight where we've gotten the molecular weight from some other kind of measurement and each standard has a retention time connected to it. So one measures the retention time from the chromatogram and in the bottom panel one plots that retention time for each peak against the logarithm of the molecular weight for that sample.

So this is how one constructs a calibration curve. First --

Q. Do you have -- go ahead, I'm sorry.

A. First you run the samples, the standards on the column, and second, you measure the elution time for each one of these peaks and you plot the data points on the X axis, you plot the retention time and on the Y axis you plot the molecular weight of that sample. So on the first peak it has a molecular weight of 100,000 daltons, so you plot the retention time that's measured versus 100,000 daltons on the Y axis and you use a log scale because that's what works for this type of measurement.

So this is the calibration curve we're talking about right here, and in order to create this curve, one needs standards and then the way one uses this information is one comes to the center of the peak, of the size exclusion peak for copolymer-1, and measures the retention time at that peak and then you come down to the calibration curve and you say the retention time of that peak corresponds to a molecular weight of 25,000 daltons.

I'll say this again if it's not clear, your Honor.

Q. Maybe we should move on. Do you have an additional slide you'd like to show the Court?

A. Yes. Because this is important. This is a fundamental concept of size exclusion chromatography. You calibrate the column using something with known molecular weights and then you use that calibration curve to get molecular weight information out of the sample that you're interested in.

So in this panel we've now calibrated the column with the second set of standards and the second set of standards don't have the same relationship of molecular weight to hydrodynamic volume. So now, the second set of standards is represented in green here, and this green point at 100,000 daltons has a retention time which is different from the retention time of the 100,000 dalton standard in the first case.

What does that mean? Well, that means that we can construct two sets, two calibration curves from the data from these two standards and then when we take that and compare it to our sample, the value of molecular weight that we get for the sample then depends on which calibration curve we can use. I think you can see that if you follow this exercise that the molecular weight results depend on which set of sample standards you use.

Q. Is this a hypothetical demonstrative?

A. It's a hypothetical demonstrative, but it parallels the situation in cop-1.

Q. Could you please turn to DTX 1930 in your binder?

A. Yes.

THE COURT: Mr. Aannestad, can you give me an idea of how much longer the direct is?

MR. AANNESTAD: We're definitely going to go into tomorrow, your Honor. I was reaching a logical stopping point in three more questions. I understand Dr. Mays is not going to be called, which gives us plenty of time to finish up tomorrow if you would like to stop now.

THE COURT: Is there any other potential witness for tomorrow?

MS. BLOODWORTH: No, our understanding was Dr. Scandella would provide the teaching that Dr. Mays would, so we've removed him from the witness list. We'll have Dr. Green on Monday.

THE COURT: All right.

MR. DOYLE: And Sandoz will rest after Dr. Scandella. Maybe some cleanup with regard to exhibits.

THE COURT: Okay. Mr. Aannestad, do you want to finish the next section or do you want to stop?

MR. AANNESTAD: I'd just like to finish up this section. It should take less than five minutes.

THE COURT: All right, go ahead.

Q. If you could turn to DTX 1930 in your binder?
A. I have it.
Q. Are you familiar with this document?
A. Yes, I am.
Q. What is this?
A. This is a book written by Robert L. Cunico, Karen Gooding and Tim Wehr on capillary electrophoresis of biomolecules. It includes a chapter on size exclusion chromatography.
Q. Do you know Dr. Cunico?
A. Yes. I know him personally and I worked with him on several projects.
Q. If you could go to figure 6.6, which is on page 128?
MR. JAMES: Your Honor, I just object to the questioning on this document. As you saw on the first page it's a 1998 document so I don't think it's relevant to what a person of skilled in the art would know in 1994.
MR. AANNESTAD: It's just exemplary, your Honor.
THE COURT: Do I need it?
MR. AANNESTAD: You don't need it. We'll see something similar later on.
THE COURT: Okay.
MR. AANNESTAD: All right, thank you, your Honor.
THE COURT: That's it?
MR. AANNESTAD: We'll continue tomorrow.
THE COURT: We're going to start tomorrow morning at

10. That will be a luxurious extra half hour. Good evening, Doctor, see you in the morning.

(Adjourned)

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